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Enantioselective Synthesis of Acyclic α-Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

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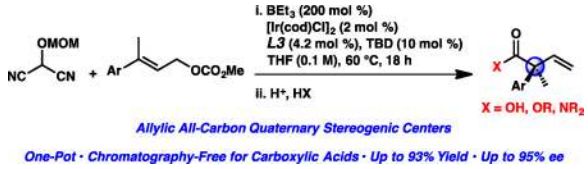
Abstract

The first highly enantioselective iridium-catalyzed allylic alkylation providing access to products bearing an allylic all-carbon quaternary stereogenic center has been developed. The reaction utilizes a masked acyl cyanide (MAC) reagent, which enables the one-pot preparation of α-quaternary carboxylic acids, esters, and amides with a high degree of enantioselectivity. The utility of these products is further explored via a series of diverse product transformations.

COMMUNICATION



Ir-resistable: The first enantioselective iridium-catalyzed allylic alkylation providing access to products bearing an allylic all-carbon quaternary stereogenic center has been developed. The reaction utilizes a masked acyl cyanide (MAC) reagent, which enables a one-pot preparation of α-quaternary carboxylic acids, esters, and amides with a high degree of enantioselectivity. The utility of these products is further explored via a series of diverse product transformations.

Keywords

Iridium; Allylic Alkylation; Umpolung; Quaternary Stereocenter; Carboxylic Acid Derivatives

The field of enantioselective iridium-catalyzed allylic alkylation has flourished in the 20 years since the seminal report by Helmchen.[1] Over these two decades, the substrate scope with respect to the nucleophile has expanded significantly to encompass a vast array of both carbon[2] and hetereoatom[3] nucleophiles.[4] Conversely, the scope of the electrophiles has remained largely unchanged, being limited to those that produce products bearing a tertiary

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Dedicated with admiration and respect to Professor Günter Helmchen on the 20th Anniversary of his seminal report on iridium-catalyzed asymmetric allylic alkylation.

allylic stereocenter (Figure 1a, left).[5] Despite the longstanding interest in the synthesis of enantioenriched quaternary stereocenters within the synthetic community as well as the development of other transition metal-catalyzed processes to access all-carbon quaternary allylic stereocenters,[6,7,8] iridium-catalyzed allylic alkylation reactions that furnish products possessing such a stereocenter remain conspicuously absent from the literature (Figure 1a, right).

As part of our ongoing program in developing iridium-catalyzed allylic alkylation technology and our continued interest in the catalytic, asymmetric synthesis of quaternary stereocenters,[9] we were attracted to this unmet challenge. Moreover, we imagined that an umpolung strategy iridium-catalyzed allylic alkylation reaction of a trisubstituted allylic electrophile with a masked acyl cyanide (MAC) nucleophile would not only give rise to products containing an enantioenriched allylic all-carbon quaternary stereocenter, but also provide access to highly valuable acyclic α-quaternary carboxylic acid derivatives (i.e., acids, esters, amides) upon unmasking of the MAC functionality (Figure 1b).[8,9e,10] However, success of this strategy hinged upon the implementation of a trisubstituted allylic electrophile, which were predicted to be unreactive in an enantioselective iridium-catalyzed allylic alkylation reaction. It is known that the reaction rates of these processes decrease with increasing substitution on the olefin of the electrophile.[5,11,12] Herein, we unlock this heretofore unreactive class of electrophiles to achieve the first example of an enantioselective iridium-catalyzed allylic alkylation reaction forming a quaternary stereocenter at the allylic position.

Preliminary studies focused on identifying a combination of ligand and additive to promote the reaction of MAC **1** and trisubstituted allylic electrophile **2** (Table 1). Application of our standard conditions for iridium-catalyzed allylic alkylation reactions of $[Ir(cod)Cl]_2$, **L1**, and LiBr returned only starting material (Table 1, entry 1).[9a,e] A brief ligand screen revealed that while ligand **L2** also resulted in no reaction (entry 2), the phosphoramidite **L3** developed by Carreira provided desired product **3** in 13% yield with a moderate 79% ee (entry 3).[3b] Attempts to further increase yield and selectivity via an extensive evaluation of additives known to promote iridium-catalyzed allylic alkylations proved ineffective.[2–4,9] As we hypothesized that the oxidative addition process is slow for trisubstituted allylic electrophiles, we reasoned that the inclusion of a strong Lewis acid would facilitate the ionization of the carbonate during the insertion event, leading to improved reactivity of these recalcitrant electrophiles. Toward this end, we substituted LiBr for triethylborane and were pleased to find that the yield nearly tripled and the enantioselectivity rose to 93% ee (entry 4).[13] Upon varying the stoichiometry of nucleophile **1** to electrophile **2**, we observed a dramatic increase in yield to 74% with no erosion of enantioselectivity (entry 5). Ultimately, we discovered that exposure of a mixture (1:2) of MAC **1** and trisubstituted allylic electrophile **2** afforded MAC adduct **3** in nearly quantitative yield and in 94% ee (entry 6).[14]

During the course of our optimization studies, we discovered both the surprising necessity of the guanidine base TBD as well as the importance of electrophile stereochemistry in our newly developed reaction. Though previously reported conditions for the use of **L3** in iridium-catalyzed allylic alkylations do not require a base additive,[15] we found the inclusion of TBD during the catalyst prestir to be critical to the success of the reaction. We

hypothesize that TBD may be serving as either a placeholder ligand to prevent the formation of an inactive catalyst[16] or as a base to promote the formation of an active iridicycle.[2a,c] Additionally, we noted that use of the *E*-trisubstituted allylic electrophile was required, as *Z*-olefin isomer **4** led to markedly decreased yield and selectivity (Table 2).[17] Moreover, neither a kinetic nor a dynamic kinetic resolution occurs under the reaction conditions with the use of terminal olefin *rac*-**5** (Table 2).

Before substrate scope exploration commenced, we identified an additional opportunity for innovation. We imagined that hydrolysis of the MAC functionality of product **3** could be performed in the same reaction vessel as the iridium-catalyzed allylic alkylation reaction to provide direct access to the corresponding carboxylic acid in a one-pot, two-step procedure.[10] Moreover, we envisioned that these carboxylic acid products would be amenable to purification by a simple acid/base extraction. To this end, we subjected the crude allylic alkylation mixture to hydrolysis with 6M HCl at 80 °C and were pleased to find that pure carboxylic acid **7a** was obtained after an aqueous work-up with no need for column chromatography (Table 3).

With the optimized protocol in hand, we first explored the effect of substitution on the aryl moiety of electrophile **6** (Table 3). We were pleased to find that *para*-substitution was well tolerated to provide acids **7b–f** in consistently high enantioselectivities, though electron-rich substrates provided decreased yields. *Meta*-substituted products **7g** and **7h** were obtained in similarly high enantioselectivites (92% and 87% ee, respectively), and bulky naphthyl-substituted acid **7i** was furnished in 92% ee, albeit in a moderate 66% yield. Further exploration of steric effects using methyl-substituted derivatives demonstrated that while a single *meta*-substituent is tolerated to access **7j** in 68% yield with 93% ee, the bis-*meta*-substituted derivative **7k** was afforded in a drastically lower 32% yield but with good enantioselectivity (85% ee). Finally, we discovered that *ortho*-substitution was not tolerated and only starting material was recovered from the reaction.[18]

With the general trends in reactivity corresponding to aryl substitution elucidated, we next turned our attention to the scope of the reaction with respect to the aliphatic moiety of the electrophile (Table 4). We found that extension of the alkyl chain led to decreased yields with ethyl-substituted **9a** and *n*-butyl-substituted **9b** isolated in 61% and 14% yield, respectively, though both were obtained in similarly excellent enantioselectivities. Furthermore, branched-substituted electrophiles were unreactive and only starting material was recovered in attempts to prepare isopropyl-substituted **9c**.

We then moved to explore the necessity of the aryl functionality. We hypothesized that cyclohexyl- and cyclohexenyl-substituted electrophiles **8d** and **8e** would mimic the sterics of the phenyl moiety of **6a** when interacting with the chiral catalyst, but we found that only trace products **9d** and **9e** were observed under our reaction conditions (Table 4). Use of bis-*n*-alkyl-substituted electrophile **8f** provided the corresponding acid **9f** in moderate yield, though no enantioselectivity was observed. Finally, we were pleased to find that prenyl methyl carbonate (**8g**) was a competent electrophile furnishing acid **9g** in 63% yield.

As MAC adducts can be transformed to essentially any carboxylic acid derivative,[10] we endeavored to develop additional one-pot transformations to access both α-quaternary esters and amides. Gratifyingly, we found that alkanolysis of the crude MAC alkylation product with either methanol or allyl alcohol provided methyl ester **10** and allyl ester **11** in 88% and 74% yield, respectively (Figure 2). Similarly, aminolysis provided access to both tertiary amide **12** in 61% yield and secondary amide **13** in 63% yield.

In order to demonstrate the synthetic utility of the enantioenriched α-quaternary carboxylic acid derivatives, a series of transformations were performed to access a diverse array of chiral building blocks starting from ester derivative **10** (Figure 3). Hydrogenation of olefin **10** delivered ethyl-substituted **14** in 97% yield. Alcohol **15** was accessed via reduction of the ester moiety in 73% yield. Dihydroxylation of the pendant olefin proceeded with concomitant lactonization to furnish γ-butyrolactone **16** in 82% yield as a mixture (1:1) of diastereomers. Finally, ozonolysis furnished aldehyde **17** in moderate yield.

In conclusion, we have developed the first synthesis of all-carbon quaternary allylic stereocenters via enantioselective iridium-catalyzed allylic alkylation. The unprecedented combination of triethylborane and a catalyst prepared from $[Ir(cod)Cl]_2$, **L3**, and TBD was used to coerce reactivity from a once poorly reactive class of trisubstituted allylic electrophiles. Furthermore, the use of a single masked acyl cyanide nucleophile facilitated the one-pot syntheses of enantioenriched α-quaternary acids, esters, and amides. The protocol is tolerant of a wide range of substitution on the aryl moiety to provide the corresponding products with good yields and excellent enantioselectivites. This methodology is critical in laying the groundwork for the future development of technology to access vicinal quaternary stereocenters via iridium-catalyzed allylic alkylation of prochiral nucleophiles. Work to elucidate the nature of this catalyst system and further expand the substrate scope will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. It should be noted that excess electrophile **2** is not consumed and can be recovered following the iridium-catalyzed allylic alkylation reaction.
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16. TBD is included with ligands **L1** and **L2** to form an active iridicycle catalyst; however, Carreira has demonstrated that ligand **L3** does not form an iridicycle, see ref. 15.

17. We rationalize this difference in reactivity via the preferred conformation of the reactants. Whereas **2** may exist in a planar conformation, the phenyl group of **4** likely prefers to rotate out of plane to alleviate $A^{1,3}$ strain. In adopting this perpendicular conformation, the phenyl ring has now increased the sterics above and below the olefin as well as become σ-withdrawing rather than π-donating.
18. Thiophene- and furan-substituted allylic electrophiles were well tolerated in the iridium-catalyzed allylic alkylation reaction but were not amenable to the hydrolysis conditions.

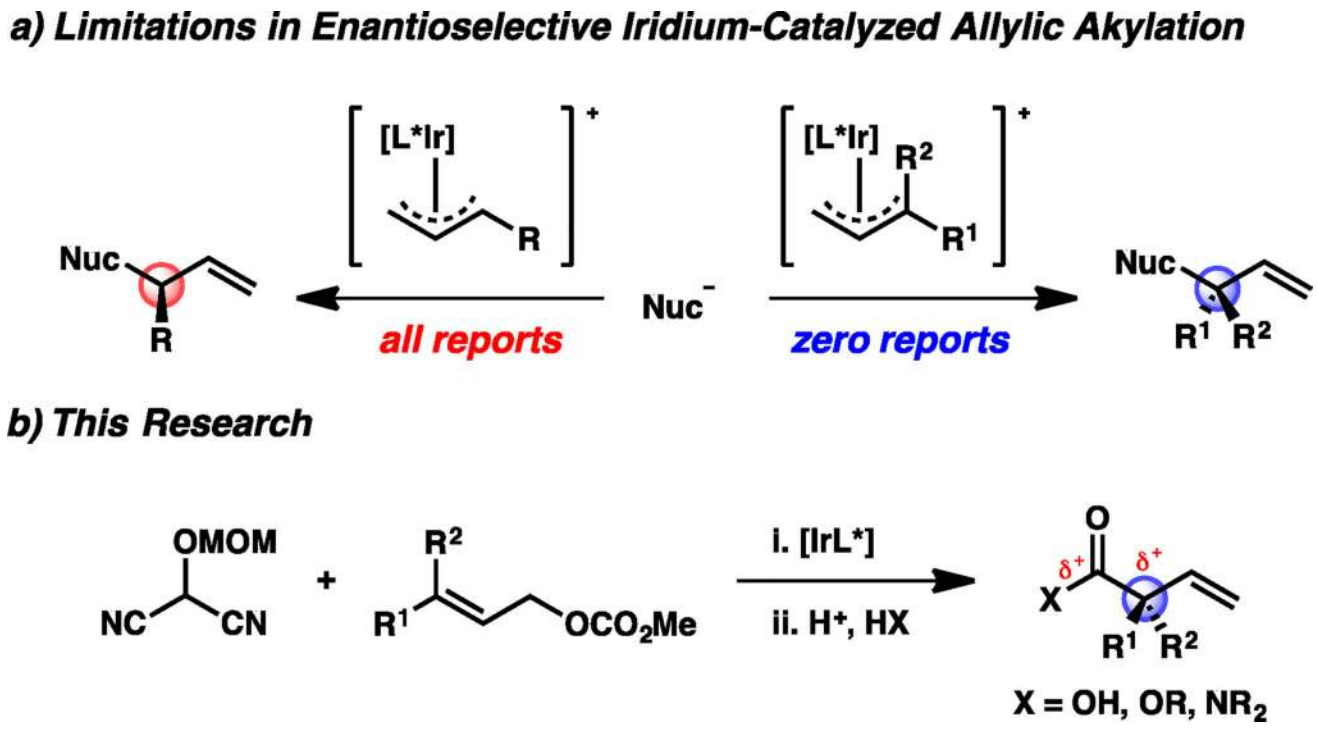


Figure 1.
Synthesis of allylic all-carbon quaternary stereocenters via enantioselective iridium-catalyzed allylic alkylation.

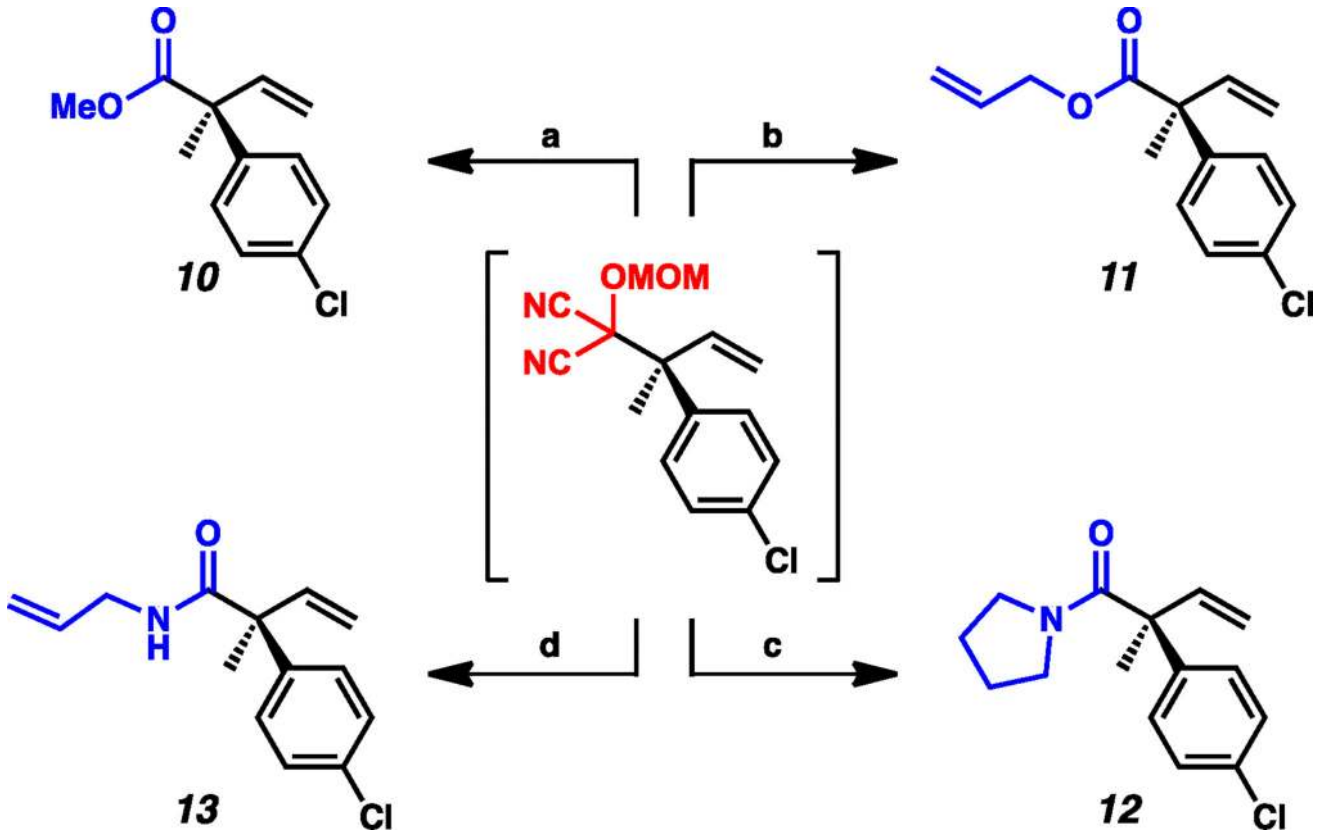


Figure 2.

(a) i. CSA, AcOH/DME, 60 °C, 6 h, ii. MeOH, Et_3N, –40 °C → 23 °C, 18 h, 88% yield; (b) i. CSA, AcOH/DME, 60 °C, 6 h, ii. allyl alcohol, Et_3N, 0 °C → 23 °C, 18 h, 74% yield; (c) CSA, AcOH/DME, 60 °C, 6 h, ii. pyrrolidine, Et_3N, –40 °C → 23 °C, 18 h, 61% yield; (d) i. CSA, AcOH/DME, 60 °C, 6 h, ii. allyl amine, Et_3N, 0 °C → 23 °C, 18 h, 63% yield.

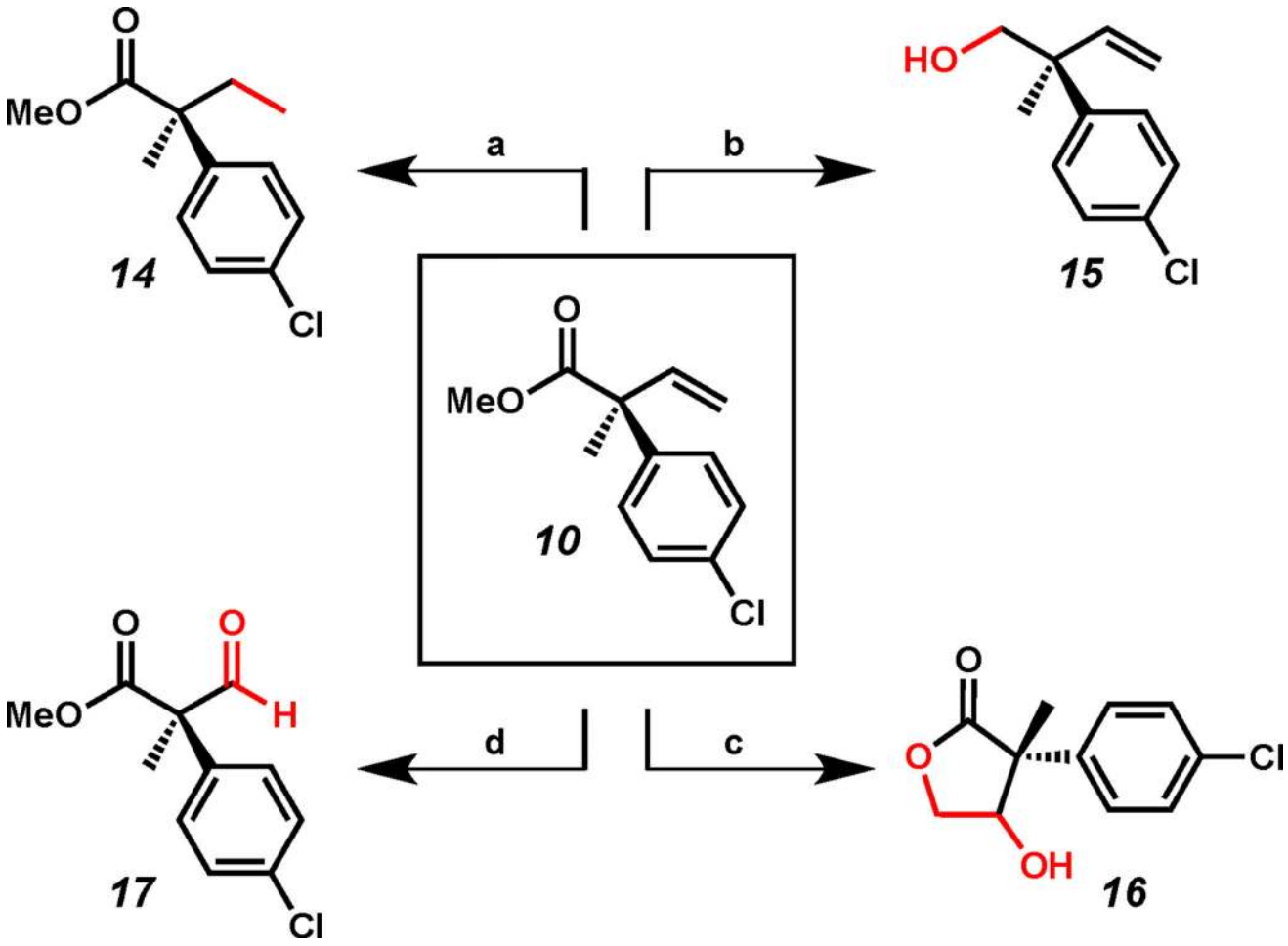
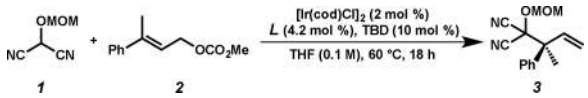


Figure 3.

(a) Pd/C, H_2 (balloon), EtOAc, 23 °C, 18 h, 97% yield; (b) DIBAL, Et_2O, 0 °C, 2 h, 73% yield; (c) K_2OsO_4, NMO, THF/H_2O (4:1), 23 °C, 18 h, 82% yield (1:1 dr); (d) i. O_3, $NaHCO_3$, MeOH/CH_2Cl_2 (1:5), −78 °C, 0.5 h, ii. DMS, −78 °C→ 23 °C, 18 h, 50% yield.

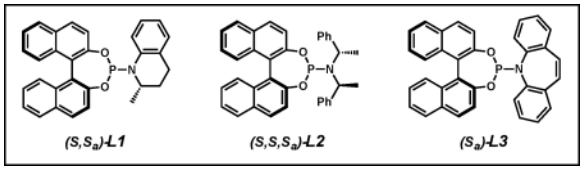
Table 1

Optimization of reaction parameters.[a]



1 *2* *3*

Entry	*L*	*1:2*	Additive (200 mol %)	Yield (%)[b]	ee (%)[c]
1	L1	2:1	LiBr	0	–
2	L2	2:1	LiBr	0	–
3	L3	2:1	LiBr	13	79
4	L3	2:1	BEt_3	34	93
5	L3	1:1.2	BEt_3	74	92
6	L3	1:2	BEt_3	99	94



[a]Reactions performed on 0.1 mmol scale.

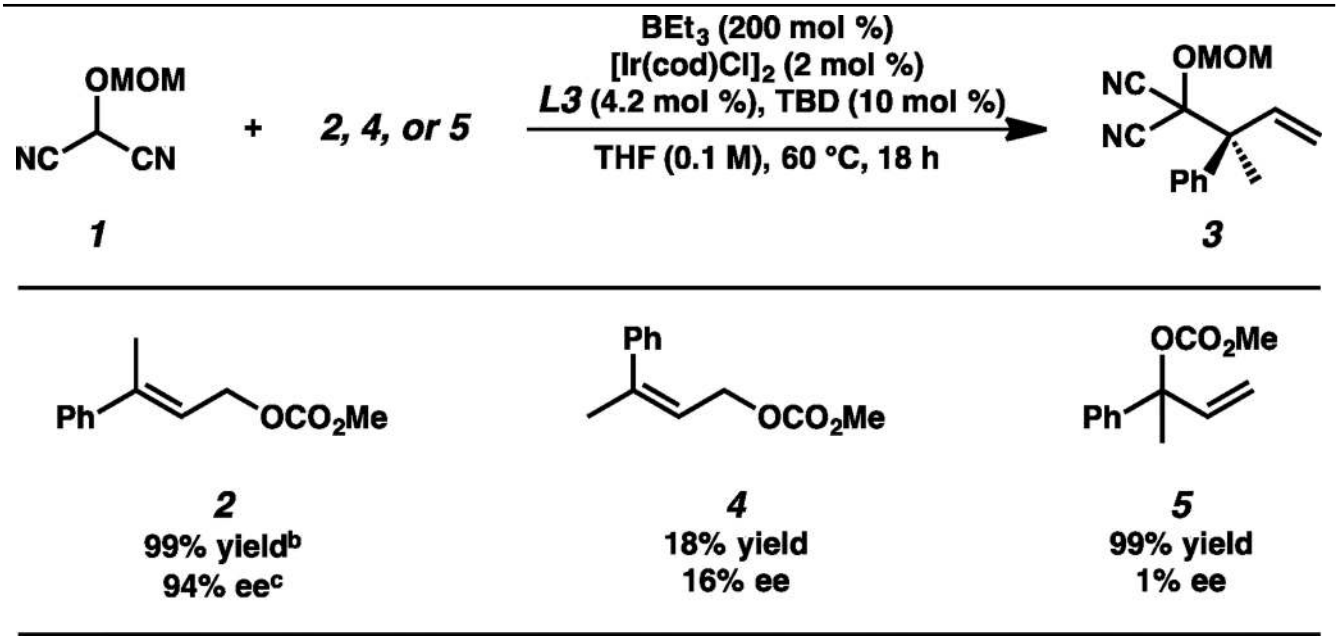
[b]^{1}H NMR yield based on internal standard.

[c]Determined by chiral HPLC analysis.

[d]TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

Table 2

Electrophile Isomers.[a]



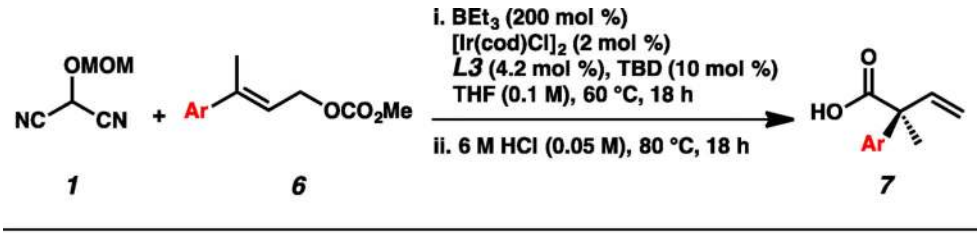
[a]Reactions performed with **1** (0.1 mmol) and **2**, **4**, or **5** (0.2 mmol).

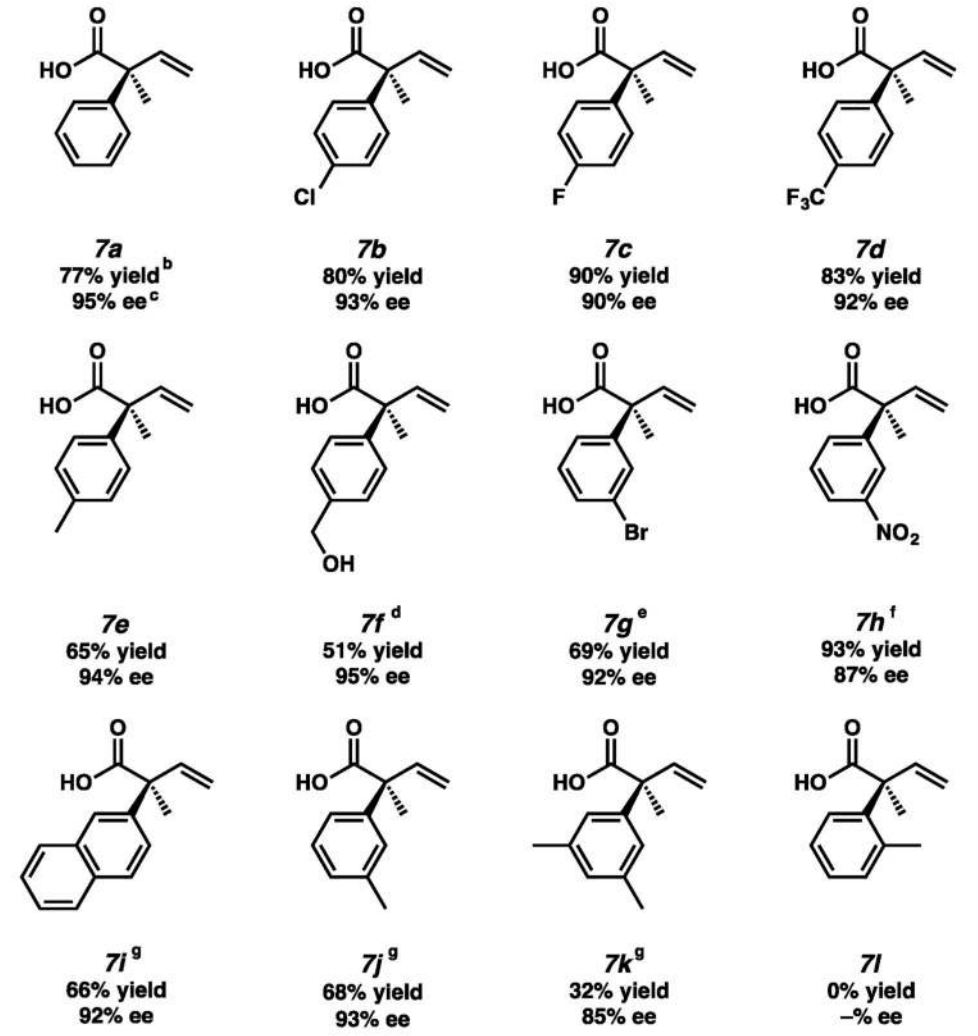
[b]^{1}H NMR yield based on internal standard.

[c]Determined by chiral HPLC analysis.

Table 3

Aryl Substituent Substrate Scope.[a]





[a] Reactions performed on 0.2 mmol scale.

[b] Isolated yield.

[c] Determined by chiral HPLC or SFC analysis.

[d] Electrophile **6f** used as the bis-carbonate which was deprotected during hydrolysis.

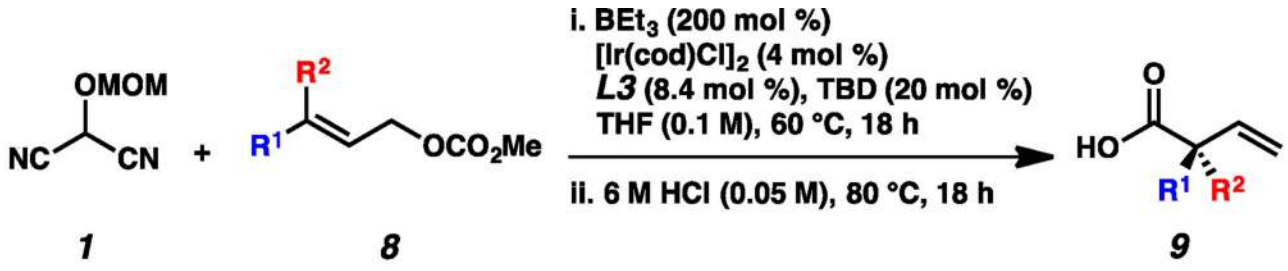
[e] Reaction run for 48 h.

[f] Absolute stereochemistry determined via single crystal X-ray analysis, the absolute stereochemistry of all other compounds has been assigned by analogy.

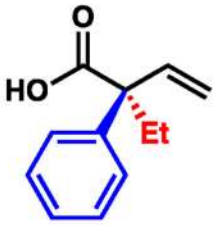
[g] Reaction performed with double catalyst loading.

Table 4

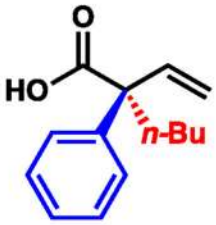
Non-Aryl Substituent Substrate Scope.[a]



1 ***8*** ***9***

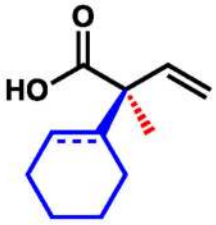


9a
61% yield[b]
92% ee[c]

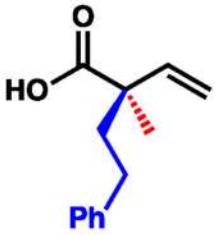


9b
14% yield
95% ee

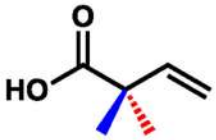
9c
0% yield
–% ee



9d/e
trace yield
–% ee



9f
32% yield
3% ee



9g
63% yield

[a]Reactions performed on 0.2 mmol scale.

[b]Isolated yield.

[c]Determined by chiral HPLC or SFC analysis.