



Published in final edited form as:

Angew Chem Int Ed Engl. 2017 September 11; 56(38): 11545–11548. doi:10.1002/anie.201707015.

## Enantioselective Synthesis of Acyclic $\alpha$ -Quaternary Carboxylic Acid Derivatives via Iridium-Catalyzed Allylic Alkylation

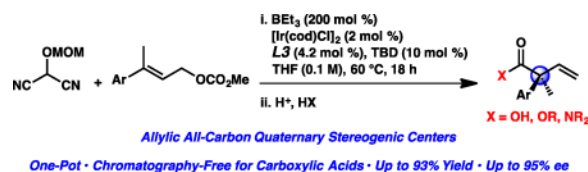
Samantha E. Shockley<sup>‡</sup>, Dr. J. Caleb Hethcox<sup>‡</sup>, and Dr. Brian M. Stoltz [Prof.]

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Blvd, MC 101-20, Pasadena, CA 91125 (USA)

### 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  $\alpha$ -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  $\alpha$ -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.<sup>1</sup> Over these two decades, the substrate scope with respect to the nucleophile has expanded significantly to encompass a vast array of both carbon<sup>2</sup> and heteroatom<sup>3</sup> nucleophiles.<sup>4</sup> Conversely, the scope of the electrophiles has remained largely unchanged, being limited to those that produce products bearing a tertiary

Correspondence to: Brian M. Stoltz.

<sup>‡</sup>These authors contributed equally.

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

allylic stereocenter (Figure 1a, left).<sup>5</sup> 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,<sup>6,7,8</sup> 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,<sup>9</sup> 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  $\alpha$ -quaternary carboxylic acid derivatives (i.e., acids, esters, amides) upon unmasking of the MAC functionality (Figure 1b).<sup>8,9e,10</sup> 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.<sup>5,11,12</sup> 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  $[\text{Ir}(\text{cod})\text{Cl}]_2$ , **L1**, and LiBr returned only starting material (Table 1, entry 1).<sup>9a,e</sup> 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).<sup>3b</sup> Attempts to further increase yield and selectivity via an extensive evaluation of additives known to promote iridium-catalyzed allylic alkylations proved ineffective.<sup>2-4,9</sup> 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).<sup>13</sup> 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).<sup>14</sup>

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,<sup>15</sup> we found the inclusion of TBD during the catalyst preiridium to be critical to the success of the reaction. We



As MAC adducts can be transformed to essentially any carboxylic acid derivative,<sup>10</sup> we endeavored to develop additional one-pot transformations to access both  $\alpha$ -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  $\alpha$ -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  $\gamma$ -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]<sub>2</sub>, **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  $\alpha$ -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 enantioselectivities. 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

The NIH-NIGMS (R01GM080269) and Caltech are thanked for support of our research program. J.C.H. thanks the Camille and Henry Dreyfus postdoctoral program, and S.E.S. thanks the NIH-NIGMS for a predoctoral fellowship (F31GM120804). Dr. Michael Takase, Dr. Lawrence Henling, and Niklas Thompson are acknowledged for assistance with X-ray analysis. Dr. Mona Shahgholi and Naseem Torian are thanked for mass spectrometry assistance. Dr. Scott Virgil is thanked for assistance with instrumentation.

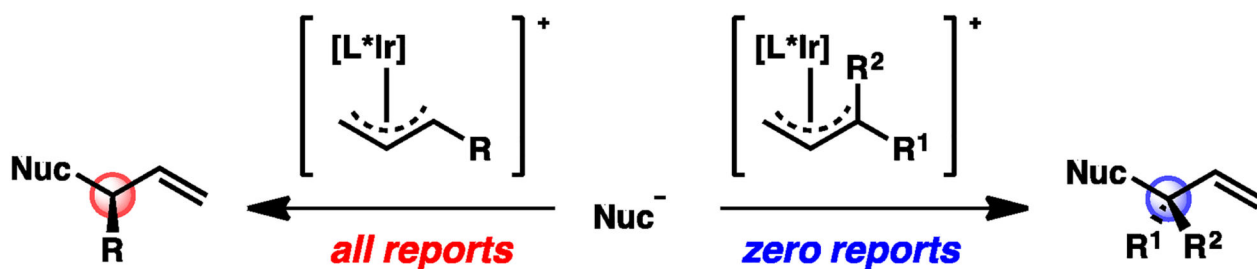
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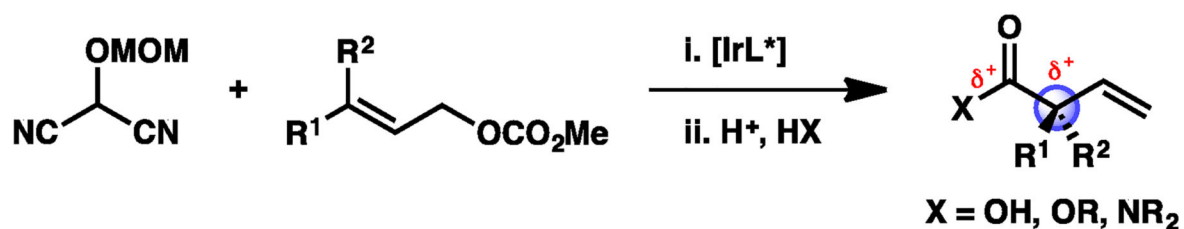
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  14. It should be noted that excess electrophile **2** is not consumed and can be recovered following the iridium-catalyzed allylic alkylation reaction.
  15. Rössler SL, Krautwald S, Carreira EM. *J. Am. Chem. Soc.* 2017; 139:3603–3606. [PubMed: 28267330]
  16. TBD is included with ligands **L1** and **L2** to form an active iridicyclic catalyst; however, Carreira has demonstrated that ligand **L3** does not form an iridicyclic, 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<sup>1,3</sup> strain. In adopting this perpendicular conformation, the phenyl ring has now increased the sterics above and below the olefin as well as become  $\sigma$ -withdrawing rather than  $\pi$ -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.

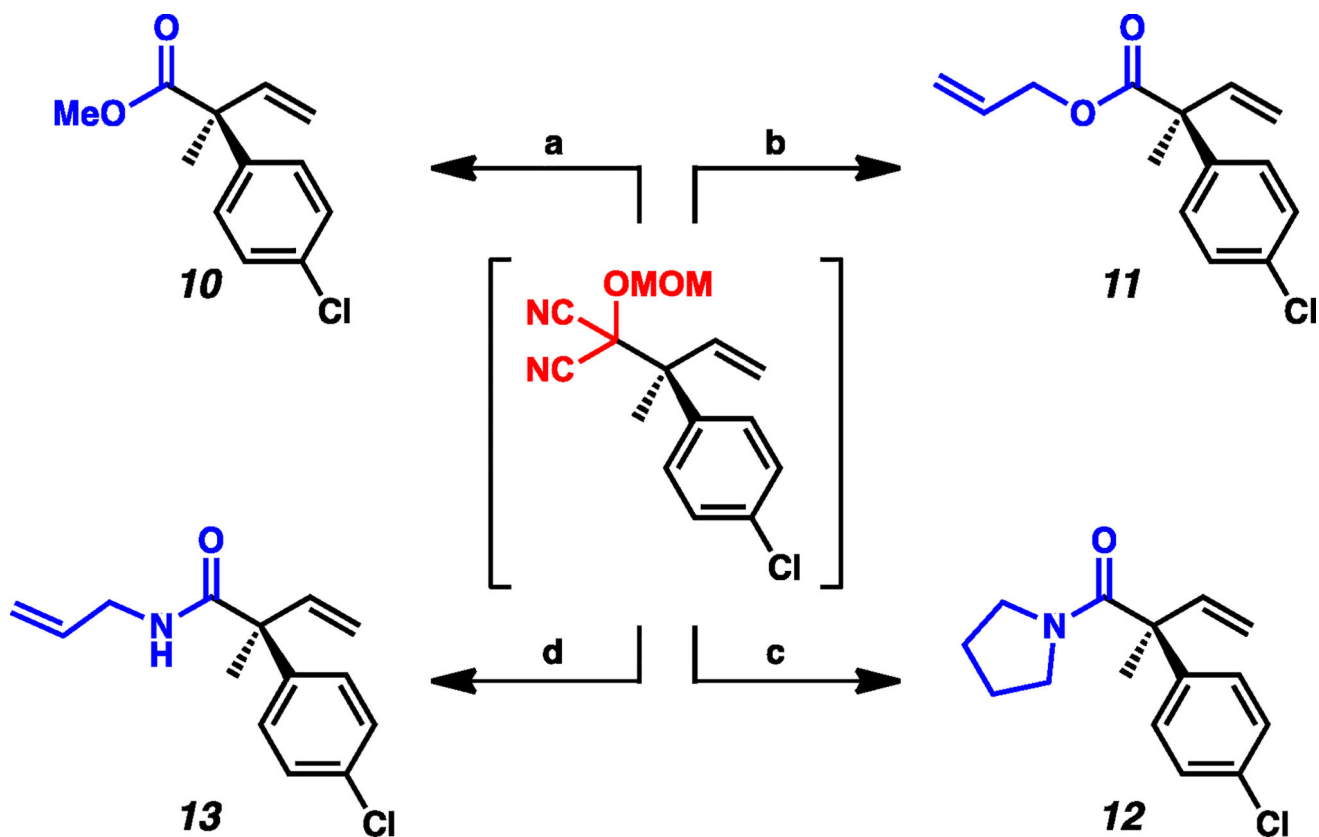
### a) Limitations in Enantioselective Iridium-Catalyzed Allylic Alkylation



### b) This Research



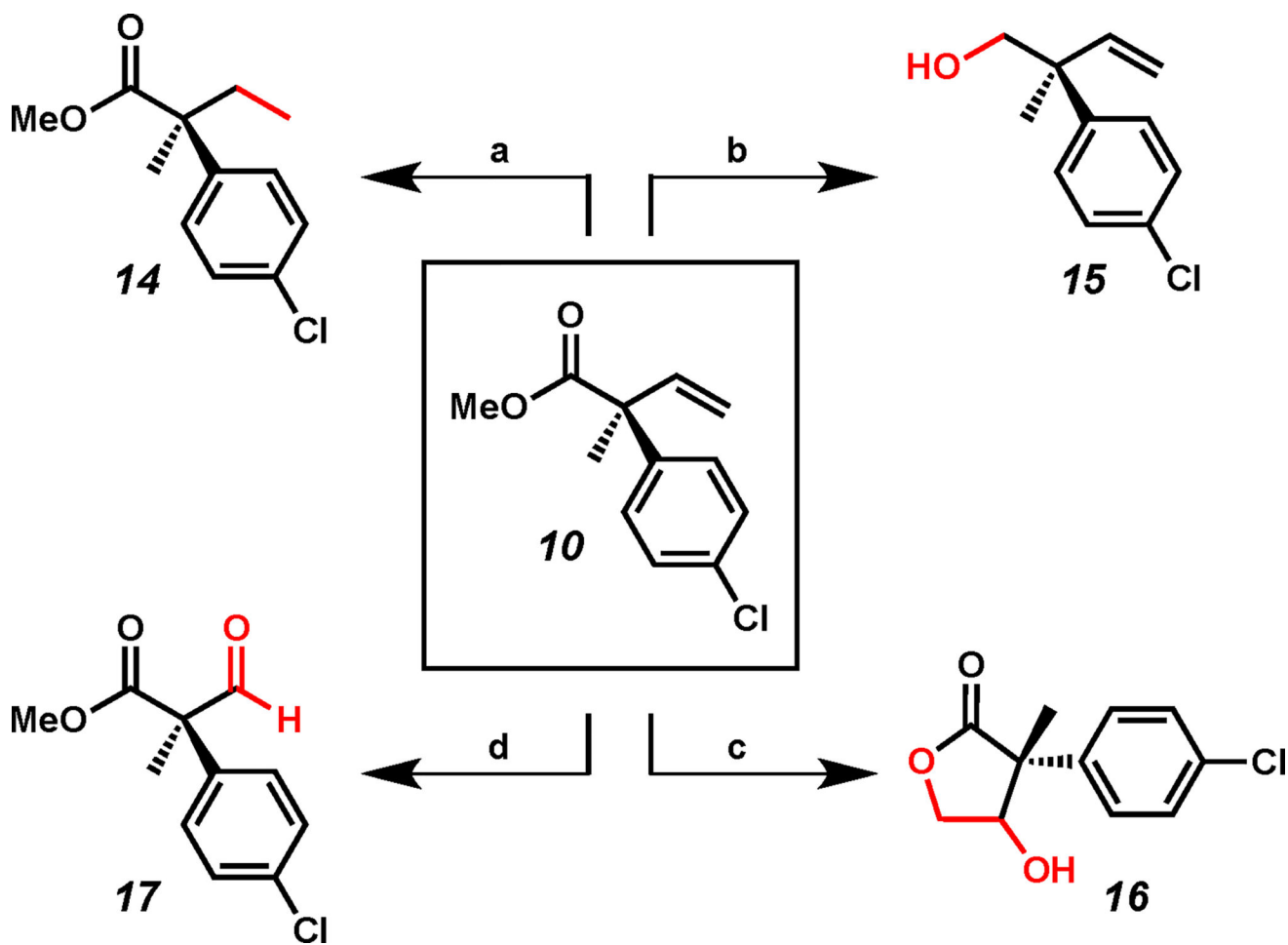
**Figure 1.** Synthesis of allylic all-carbon quaternary stereocenters via enantioselective iridium-catalyzed allylic alkylation.



**Figure 2.**

(a) i. CSA, AcOH/DME, 60 °C, 6 h, ii. MeOH, Et<sub>3</sub>N, -40 °C → 23 °C, 18 h, 88% yield; (b) i. CSA, AcOH/DME, 60 °C, 6 h, ii. allyl alcohol, Et<sub>3</sub>N, 0 °C → 23 °C, 18 h, 74% yield; (c) CSA, AcOH/DME, 60 °C, 6 h, ii. pyrrolidine, Et<sub>3</sub>N, -40 °C → 23 °C, 18 h, 61% yield; (d) i. CSA, AcOH/DME, 60 °C, 6 h, ii. allyl amine, Et<sub>3</sub>N, 0 °C → 23 °C, 18 h, 63% yield.



**Figure 3.**

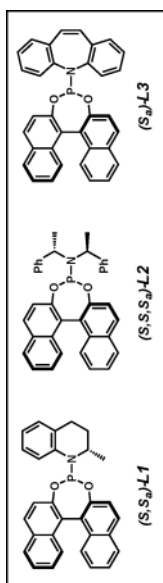
(a) Pd/C, H<sub>2</sub> (balloon), EtOAc, 23 °C, 18 h, 97% yield; (b) DIBAL, Et<sub>2</sub>O, 0 °C, 2 h, 73% yield; (c) K<sub>2</sub>OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O (4:1), 23 °C, 18 h, 82% yield (1:1 dr); (d) i. O<sub>3</sub>, NaHCO<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:5), -78 °C, 0.5 h, ii. DMS, -78 °C → 23 °C, 18 h, 50% yield.

Table 1

Optimization of reaction parameters.<sup>a</sup>



Entry	L	L : I : 2	Additive (200 mol %)	Yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	L1	2:1	LiBr	0	–
2	L2	2:1	LiBr	0	–
3	L3	2:1	LiBr	13	79
4	L3	2:1	BEt <sub>3</sub>	34	93
5	L3	1:1:2	BEt <sub>3</sub>	74	92
6	L3	1:2	BEt <sub>3</sub>	99	94



<sup>[a]</sup>Reactions performed on 0.1 mmol scale.

<sup>[b]</sup><sup>1</sup>H NMR yield based on internal standard.

<sup>[c]</sup>Determined by chiral HPLC analysis.

<sup>[d]</sup>TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

Table 2

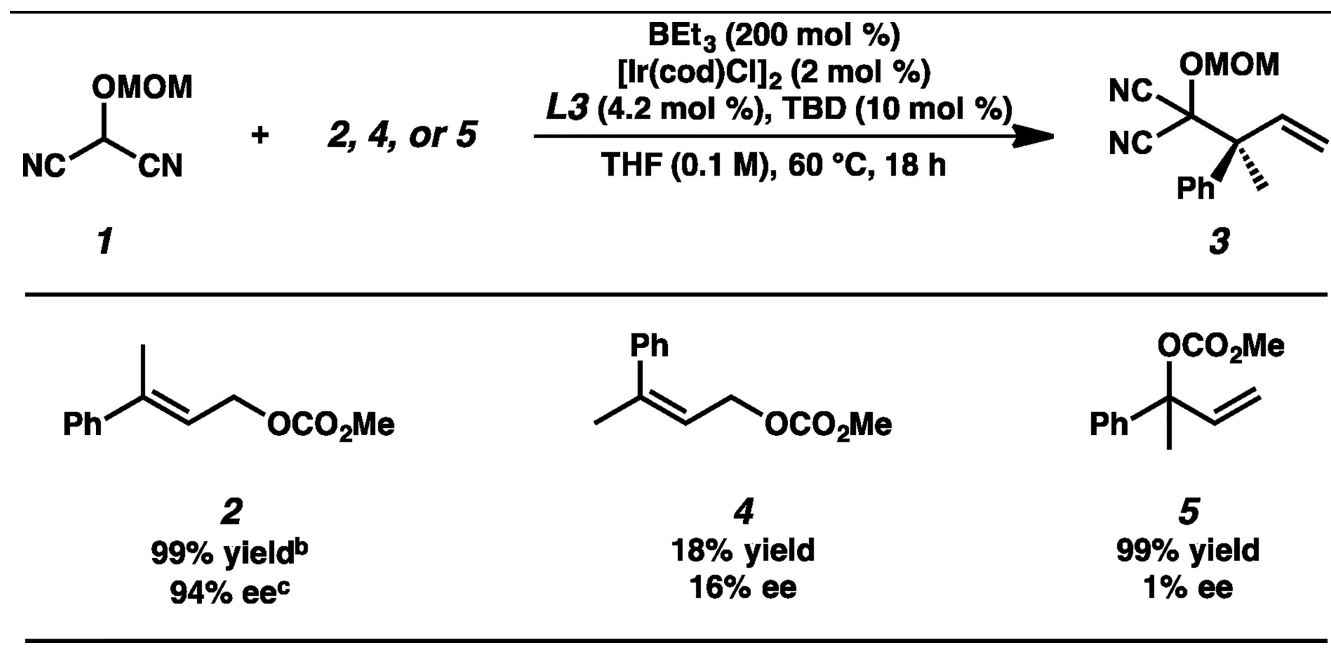
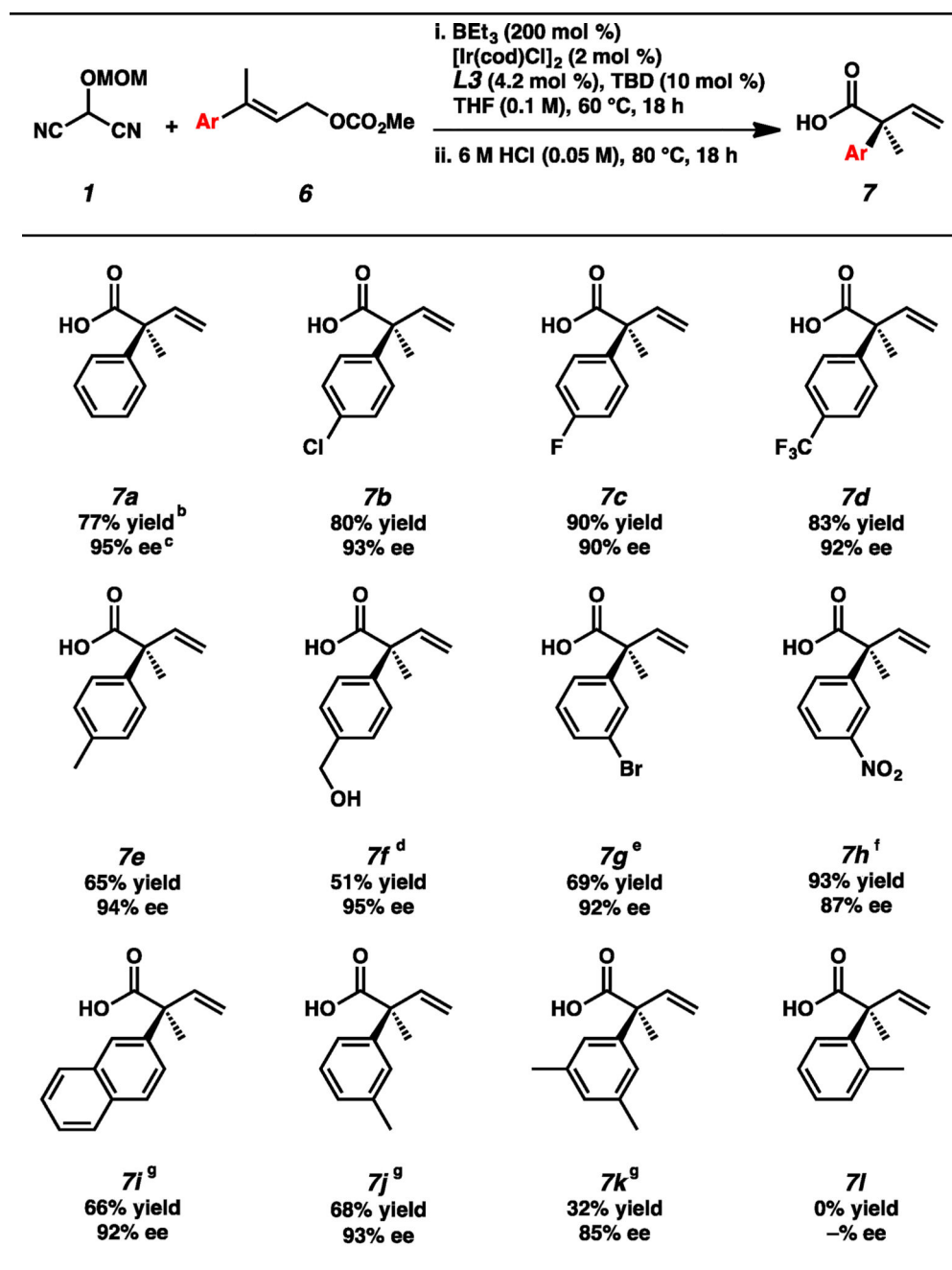
Electrophile Isomers.<sup>a</sup><sup>[a]</sup>Reactions performed with **1** (0.1 mmol) and **2**, **4**, or **5** (0.2 mmol).<sup>[b]</sup><sup>1</sup>H NMR yield based on internal standard.<sup>[c]</sup>Determined by chiral HPLC analysis.

Table 3

Aryl Substituent Substrate Scope.<sup>a</sup><sup>[a]</sup> Reactions performed on 0.2 mmol scale.<sup>[b]</sup> Isolated yield.<sup>[c]</sup> 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.

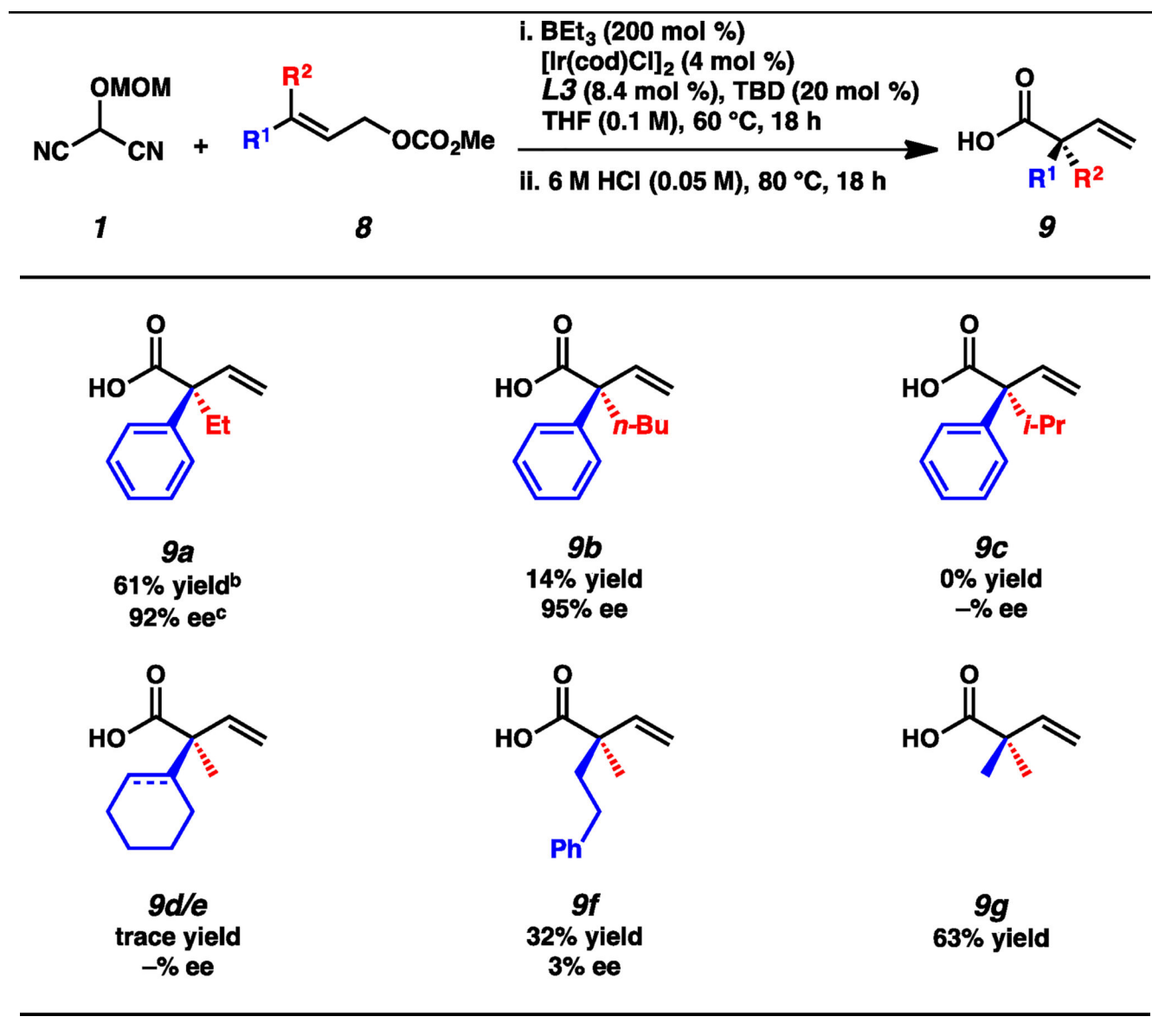
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Table 4

Non-Aryl Substituent Substrate Scope.<sup>a</sup><sup>[a]</sup>Reactions performed on 0.2 mmol scale.<sup>[b]</sup>Isolated yield.<sup>[c]</sup>Determined by chiral HPLC or SFC analysis.