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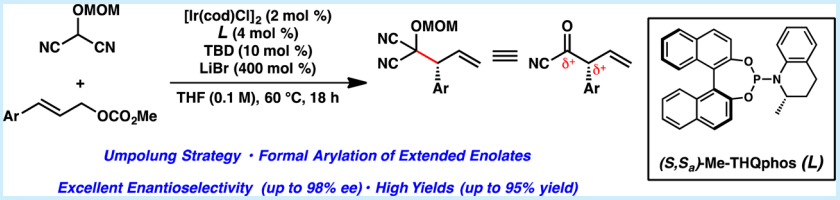
Enantioselective Iridium-Catalyzed Allylic Alkylation Reactions of Masked Acyl Cyanide Equivalents

J. Caleb Hethcox,[‡] Samantha E. Shockley,[‡] and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

Supporting Information



ABSTRACT: The first enantioselective iridium-catalyzed allylic alkylation reaction of a masked acyl cyanide (MAC) reagent has been developed. The transformation allows for the use of an umpoled synthon, which serves as a carbon monoxide equivalent. The reaction proceeds with good yield and excellent selectivity up to gram scale for a wide range of substituted allylic electrophiles, delivering products amenable to the synthesis of highly desirable, enantioenriched vinylated α-aryl carbonyl derivatives.

Since the first report of an asymmetric iridium-catalyzed allylic alkylation in 1997,[1] the technology has been widely developed for normal reactivity patterns between electrophilic π-allyl species and nucleophilic enolate equivalents, organometallic reagents, or heteroatoms (Figure 1a).[2] However, the application of an umpolung strategy to stitch together a formally electrophilic group and a π-allyl cation via enantioselective iridium-catalyzed allylic alkylation remains underexplored (Figure 1b, left).[3] To date, only two examples of reverse-polarity nucleophiles in iridium-catalyzed allylic alkylation have been reported (Figure 1b, right). In 2008, Helmchen showed that the extensively explored malononitrile nucleophile could operate as a methoxy carbonyl synthon with the subsequent application of an oxidative degradation process.[4] More recently, Carreira disclosed the use of formaldehyde *N,N*-dialkylhydrazone as a formyl anion equivalent in iridium-catalyzed allylic alkylation reactions.[5] Herein, we disclose the first use of an acyl cyanide equivalent in asymmetric iridium-catalyzed allylic alkylation, which formally serves as the addition of carbon monoxide (Figure 1c, left).

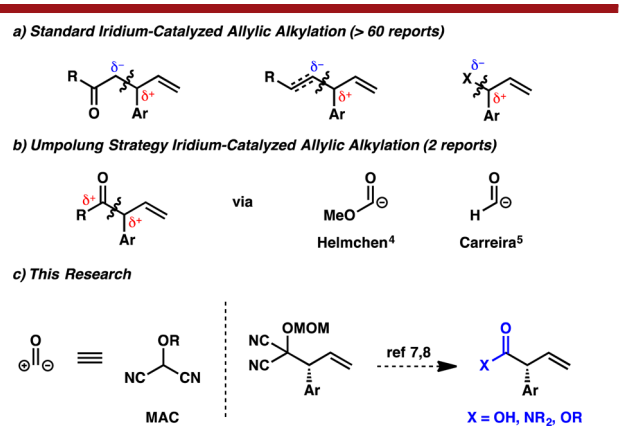


Figure 1. Iridium-catalyzed allylic alkylation strategies.

As part of our ongoing research program to develop iridium-catalyzed allylic alkylation methods,[6] we became interested in exploring the reactivity of masked acyl cyanide (MAC) reagents as reverse-polarity nucleophiles with π-allyl electrophiles. Following reaction with an electrophile, these umpoled synthons, developed by Yamamoto and Nemoto,[7] can be unmasked to reveal a transient acyl cyanide intermediate, which can be further transformed into a carboxylic acid, amide, or ester.[7,8] We envisioned that the novel application of MAC reagents to iridium-catalyzed allylic alkylation chemistry could provide access to highly desirable, enantioenriched vinylated α-aryl carbonyl derivatives, which are otherwise difficult to prepare (Figure 1c, right).[9]

Preliminary studies focused on the identification of a suitable protecting group for MAC nucleophile **1** in order to achieve the allylic alkylation reaction. Using our previously reported conditions for iridium-catalyzed allylic alkylations with cinnamyl-derived electrophiles as a starting point,[6a,10] we found that the reaction of either silyl ether **1a** or acetate **1b** with cinnamyl carbonate (**2**) furnished desired products **4a** and **4b**, respectively, albeit in low yields (Table 1, entries 1 and 2). However, the use of methoxymethyl ether **1c** provided allylic

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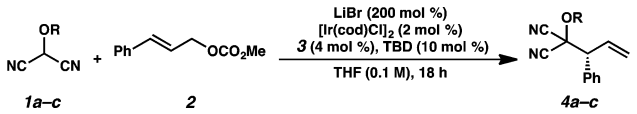
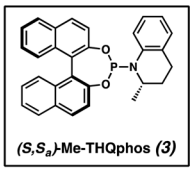
Table 1. Optimization of Reaction Parameters[a,e]



entry	R	1:2	temp (°C)	yield (%)[b]	ee (%)[c]
1	TBS (**1a**)	1:2	23	24	–
2	Ac (**1b**)	1:2	23	19	–
3	MOM (**1c**)	1:2	23	64	95
4	MOM (**1c**)	1:1	23	50	96
5	MOM (**1c**)	2:1	23	77	96
6[d]	MOM (**1c**)	2:1	23	85	97
7	MOM (**1c**)	2:1	60	86	96



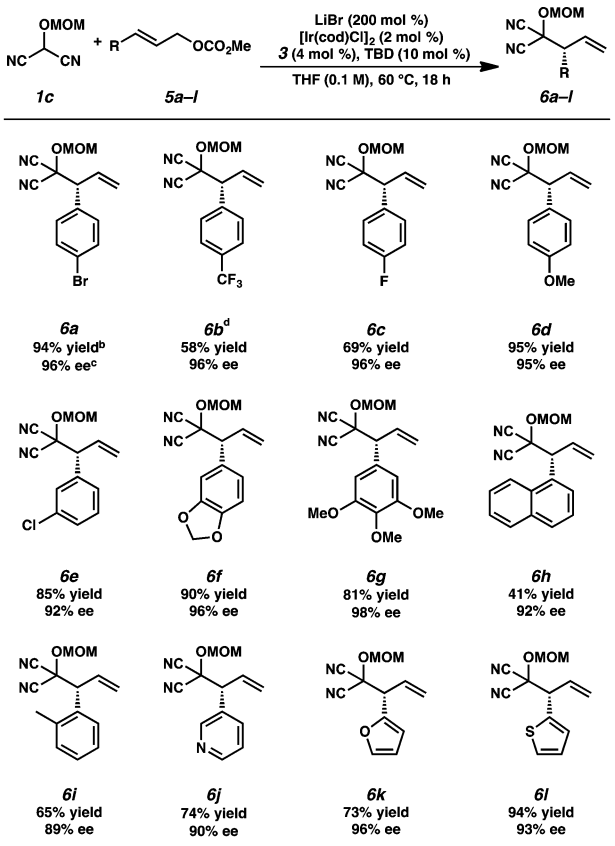
[a]Reactions performed on 0.1 mmol scale. [b]^{1}H NMR yield based on internal standard. [c]Determined by chiral HPLC analysis. [d]Reaction run for 48 h. [e]TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene.

alkylation product **4c** in 64% yield (entry 3). Moreover, we were pleased to find that product **4c** was obtained with excellent enantioselectivity (95% ee), obviating the need for further optimization beyond that of conversion. Efforts to increase the reaction conversion revealed that altering the nucleophile-to-electrophile ratio from 1:2 to 2:1 improved the yield to 77% with no erosion of enantioselectivity (entries 4 and 5). We observed that extending the reaction time from 18 to 48 h provided product **4c** in a now synthetically useful 85% yield and 97% ee (entry 6). Ultimately, we found that treatment of a mixture (2:1) of nucleophile **1c** and electrophile **2** with a combination of catalytic Ir(cod)Cl·**3** (4 mol %) and LiBr (200 mol %) at 60 °C delivered allylic alkylation product **4c** in a high 86% yield with an exceptional 96% enantioselectivity in only 18 h (entry 7).

With the optimized conditions identified, the substrate scope of the enantioselective umpolung reaction was explored (Scheme 1).[11] Our investigation began by probing the effects of electronics on reaction yield and selectivity. Gratifyingly, we observed that *para*-substituted aryl electrophiles bearing both electron-withdrawing (−Br, −CF_3, −F) and electron-donating (−OMe) groups furnished products **6a**−**d** with consistently excellent enantioselectivities (>95% ee). While products **6a** (−Br) and **6d** (−OMe) were obtained in high yield (>94% yield), diminished yields (58% and 69% yield, respectively) were obtained for the more electron-poor products **6b** (−CF_3) and **6c** (−F). Further examination of electrophile electronics revealed that *meta*-Cl-substituted **6e**, as well as polyalkoxylated **6f** and **6g**, were each furnished in good yields (>81%) and high enantioselectivities (92−98% ee), despite varying electronics. Studies involving sterically demanding substrates showed that products **6h** (−2-Np) and **6i** (−*ortho*-Me) could be provided with good selectivities (92% and 89% ee, respectively), albeit in moderate yields (41% and 65%, respectively). Additionally, we were pleased to discover that pyridine **6j**, furan **6k**, and thiophene **6l** could each be afforded with excellent enantioselectivities (90−96% ee) and in moderate to high yields (73−94%). To demonstrate the synthetic utility of this method, a preparatory scale (4 mmol) reaction was performed (Scheme 2). Using cinnamyl carbonate (**2**), both the yield and enantioselectivity of the reaction were unchanged from those obtained at 0.1 mmol scale.

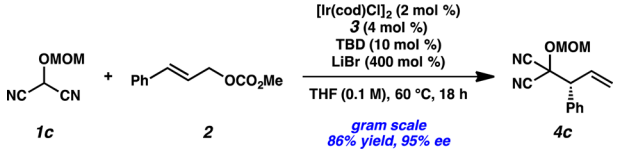
In summary, we have developed the first enantioselective iridium-catalyzed allylic alkylation reaction of masked acyl cyanide (MAC) reagents. The umpolung strategy showcased in this reaction diverges from the normal reactivity patterns employed in all but two of the previously reported iridium-catalyzed allylic alkylations and is the first report of a carbon monoxide synthon in iridium-catalyzed allylic alkylation. Critical to the success of this new reaction is the identity of the methoxymethyl protecting group on the MAC reagent. The developed methodology proceeds with moderate to excellent yields (up to 95%) and high levels of enantioselectivity (up to 98% ee) up to gram scale for a wide range of aryl- and heteroaryl-substituted allylic electrophiles. Furthermore, MAC adducts bearing resemblance to compound **4c** have been transformed into acids, amides, and esters by unmasking the alkoxy malononitrile moiety.[7,8] Thus, this methodology serves as an entry to enantioenriched vinylated α-aryl carbonyl derivatives. Further explorations to expand the scope of this chemistry to include additional electrophile classes are currently underway and will be reported in due course.

Scheme 1. Electrophile Substrate Scope[a]



[a]Reactions performed on 0.2 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC or SFC analysis. [d]Reaction run for 36 h at 50 °C.

Scheme 2. Preparatory Scale Reaction



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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS), and SFC/HPLC data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stoltz@caltech.edu.

ORCID

Brian M. Stoltz: 0000-0001-9837-1528

Author Contributions

‡J.C.H. and S.E.S. contributed equally.

Notes

The authors declare no competing financial interest.

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(10) As in ref 6a, LiBr was found to improve the regioselectivity of the allylic alkylation reaction. The use of 200 mol % (in comparison to 100 mol % as in ref 6a) provided consistently higher yields of the branched product.

(11) The optimized reaction conditions failed to provide high regioselectivities when aliphatic-substituted allylic electrophiles were employed.

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