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β-Lactam Synthesis via Copper-Catalyzed Directed Aminoalkylation of Unactivated Alkenes with Cyclobutanone *O*-Benzoyloximes

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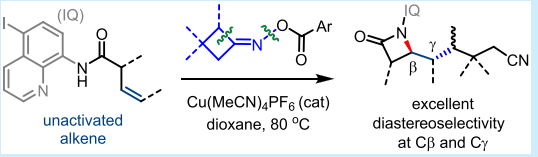
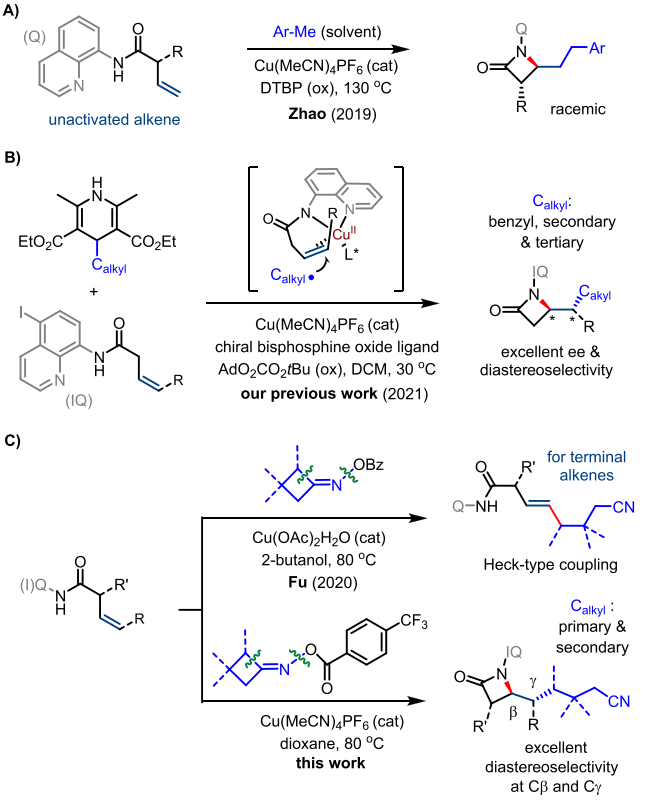
ABSTRACT: A new protocol for amide-directed Cu-catalyzed aminoalkylation of unactivated alkenes using cyclobutanone oxime esters as alkyl radical donors is developed. Both primary and secondary alkyl groups can be selectively installed at the C4 position of terminal or *cis*-internal 3-alkenamides in moderate to good yield. This reaction offers a useful method for the diastereoselective synthesis of β-lactams bearing 4-cyanoalkyl β-substituents. The use of a weakly coordinating counteranion as the Cu catalyst is critical for the formation of β-lactam products.



The field of metal-catalyzed functionalization of alkenes has greatly advanced over the past few decades, offering streamlined access to various synthetically useful carbon frameworks.[1] In comparison to activated alkenes, functionalization of unactivated alkenes remains challenging.[2] Recently, substrate-directed approaches have emerged as an effective strategy for facilitating metal-catalyzed functionalization of unactivated alkenes.[3−9] While the installation of aryl groups on alkenes has been achieved under various metal catalyses, the installation of alkyl groups on alkenes is much less developed. Notably, the Zhao group reported a novel radical-mediated amino-benzylation reaction of alkenes with benzyl radicals generated from methylarene solvents under Cu catalysis using an aminoquinoline (AQ) auxiliary (Scheme 1A).[8] It was proposed that the addition of benzyl radicals to the alkene forms an AQ-chelated Cu^{III}-metallacycle intermediate, which then gives the β-lactam product following the intramolecular C−N reductive elimination.[10,11] Recently, we reported an enantioselective version of this reaction using 4-alkyl Hantzsch esters as the donor of alkyl radicals, a biaryl diphosphine oxide ligand as the chiral ligand, and peroxycarbonate as the oxidant (Scheme 1B).[12] The reaction worked well for benzyl and normal secondary and tertiary alkyl groups, whereas the primary alkyl groups gave a low yield. Herein, we report a new protocol for this auxiliary-directed Cu-catalyzed aminoalkylation of unactivated alkenes using cyclobutanone oxime esters as the donor of alkyl radicals (Scheme 1C). Both primary and secondary alkyl groups can be installed. This reaction offers a useful method for diastereoselective synthesis of β-lactams bearing various 4-cyanoalkyl β-substituents.[13]

While the 4-alkyl Hantzsch esters serve as an excellent alkyl radical precursor in our previous enantioselective reaction system, the need for an external oxidant and the poor performance of primary alkyl groups prompted us to explore other types of alkyl donors. Recently, cycloketone oxime esters have emerged as very effective alkyl donors that can be readily formed by the cleavage of the N−O bond by single-electron

Scheme 1. Synthesis of β-Lactam via Copper-Catalyzed Directed Aminoalkylation of Unactivated Alkenes



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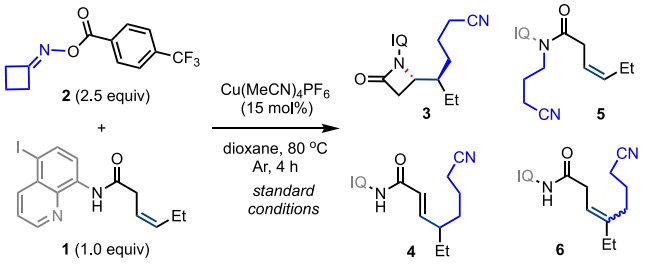
transfer and the subsequent β C−C scission.[14−16] These alkyl groups have been successfully utilized in the additions to alkenes and arenes and in the other C−C and C−heteroatom coupling reactions. In particular, the Fu group reported that the 3-cyanoalkyl groups can be selectively added at the γ position of AQ-coupled 3-butenamides to give Heck-type *trans*-substituted alkene products using a $Cu(OAc)_2{\cdot}H_2O$ catalyst in a 2-butanol solvent (Scheme 1C).[9] Unlike Zhao's system, an unusual benzoate ligand-facilitated β elimination of a Cu^{III} intermediate was proposed for the formation of the alkylated alkene product.

Intrigued by Fu's study, we wondered whether the cycloketone oxime esters can be employed in our system to form the β-lactam product under modified conditions. As shown in Table 1, the model reaction of *cis*-3-hexenamide **1**

Table 1. Optimization of the Reaction of 1 with 2[a]



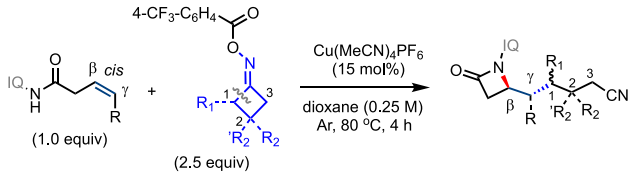
entry	deviation from standard conditions	yield (%) (3/5/4+6/1)
1	none	67 (60[b])/28/0/0
2	$Cu(OAc)_2$ as the catalyst	trace/22/46/25
3	CuOAc as the catalyst	trace/19/56/19
4	CuI as the catalyst	trace/7/37/43
5	CuOTf as the catalyst	60/32/0/0
6	$Cu(MeCN)_4BF_4$ as the catalyst	60/24/0/10
7	dichloromethane as the solvent	47/31/0/20
8	THF as the solvent	45/26/0/18
9	2-BuOH as the solvent	42/26/0/14
10	DCE as the solvent	40/25/0/15
11	rt	20/10/0/57
12	50 °C	58/28/0/10
13	under air	54/30/0/0
14	with TEMPO	0/0/0/95
15	with the BINAPO ligand	32 (14% ee)/35/0/16
16	IQ replaced with AQ	52/43/0/0
17	IQ replaced with 5-chloro-8-aminoquinoline	66/29/0/0
18	4-CF_3-C_6H_4CO replaced with Bz	49/15/0/15
19	with 10 mol % Cu	60/30/0/0
20	*trans*-alkene isomer of **1**	trace/47/0/45

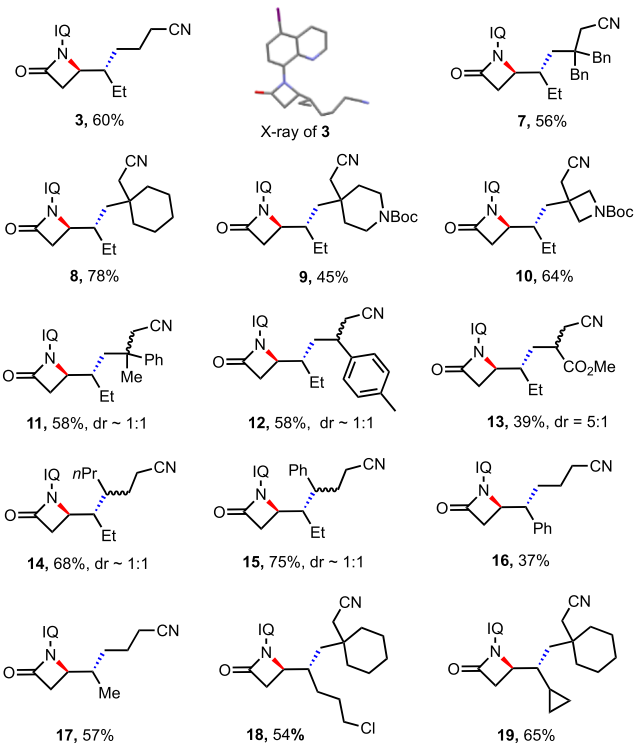
[a]Yields were based on ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard on a 0.1 mmol scale. [b]Isolated yield. Reaction on a 1 mmol scale gave **3** in 52% isolated yield. See the Supporting Information for additional optimization results.

bearing a 5-iodoquinoline auxiliary with cyclobutanone oxime ester **2** bearing a *p*-CF_3-benzoyl group gave the desired β-lactam product **3** in 60% isolated yield with exclusive *anti*-diastereoselectivity along with 28% of N-alkylation product **5** using the $Cu(MeCN)_4PF_6$ catalyst in dioxane at 80 °C (entry 1). Notably, little Heck-type product **6** was formed. The use of Cu catalysts bearing other weakly coordinating counteranions such as OTf and BF_4 gave similar results (entries 5 and 6, respectively). In contrast, the use of a Cu catalyst bearing strongly coordinating anions such as OAc and iodide gave a small amount of lactam product **3**, instead, forming a mixture of **5**, **4**, and **6** along with recovered **1**. Other solvents such as dichloroethane (DCE), THF, and 2-BuOH gave lower yields of **3** (entries 7−10). The addition of the (2,2,6,6-tetramethylpiperidin-1-yl)oxyl oroxidanyl (TEMPO) reagent abolished the formation of **3**, primarily generating the O-alkylation product of TEMPO (entry 14). Addition of chiral BINAP oxide (BINAPO) gave **3** in lower yield with low enantioselectivity (entry 15). As seen in our previous system, the incorporation of an iodo group at position 5 of aminoquinoline increases the β-lactam selectivity (entries 16 and 17).[17] The ester group of cyclobutanone oximes also had a significant impact on the reaction. The *p*-CF_3-benzoyl group showed the best yield and chemoselectivity (entry 18, and see the results for other analogues in the Supporting Information). The *trans*-alkene substrate gave little β-lactam product (entry 20).

With the optimized conditions in hand, we next examined the scope of cyclobutanone oxime esters and alkenes (Scheme 2). Cyclobutanone oxime esters bearing equivalent substituents at C_2 worked well, giving the desired β-lactam products (**7**−**10**) in moderate to good yields with exclusive *anti*-

Scheme 2. Scope of *cis*-Alkenes and Cyclobutanone Oxime Esters[a]





[a]Isolated yields on a 0.1 mmol scale. *cis*-Alkene substrates were used unless otherwise specified.

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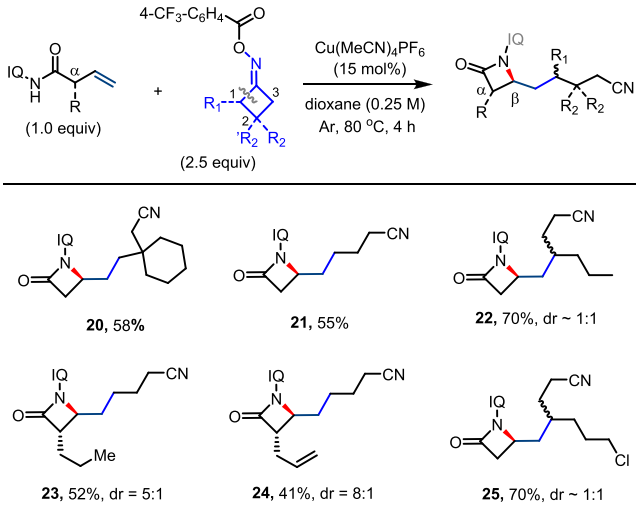
diastereoselectivity. Reactions of cyclobutanone oxime esters bearing non-equivalent substituents at C_2 gave products as a mixture of diastereoisomers in moderate yields (**11**–**13**). Reactions of oxime esters bearing one substituent at C_1 also gave products as a roughly 1:1 diastereomeric mixture (**14** and **15**). As shown by **14**–**19**, alkyl, phenyl, and cyclopropyl substituents at the γ position of *cis*-3-alkenamides are tolerated.

As shown in Scheme 3, terminal alkenes also worked well under the standard conditions. Reaction of plain 3-butenamide

Scheme 3. Reactions of Terminal Alkenes[a]

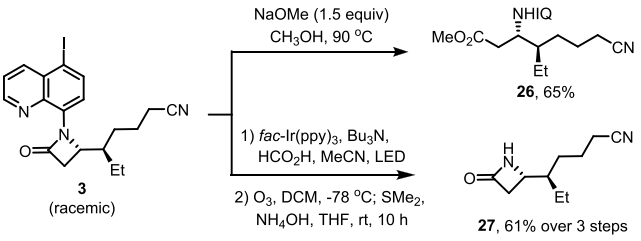


[a]Isolated yields on a 0.1 mmol scale.

with oxime esters bearing one substituent at C_1 gave products as a roughly 1:1 diastereomeric mixture (**22** and **25**). Reaction of α-substituted 3-butenamide with unsubstituted cyclobutanone oxime esters gave α,β-*trans*-substituted β-lactams in moderated yields (**23** and **24**) with moderate diastereoselectivity.

As shown in Scheme 4, treatment of compound **3** with NaOMe in MeOH at 90 °C gave acyclic β-amino ester **26** in

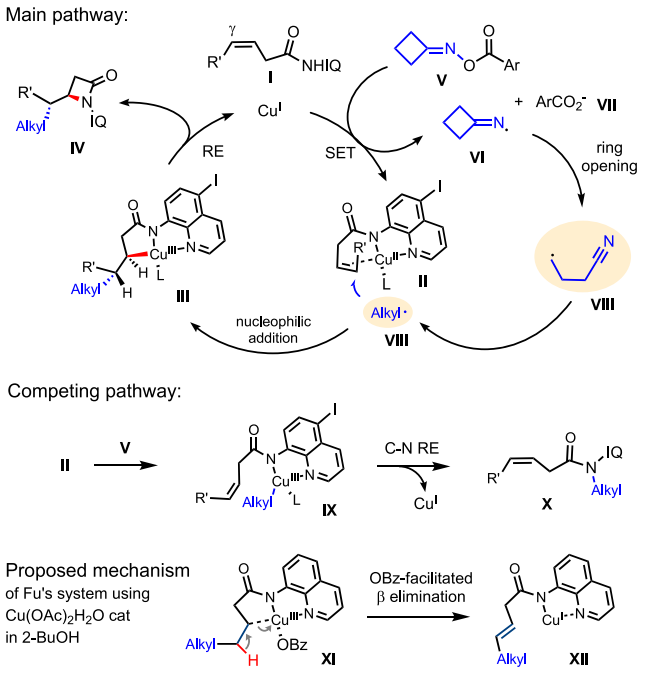
Scheme 4. Representative Transformations of β-Lactam 3



good yield. The IQ group of **3** can be removed via a three-step sequence to give **27**: photoredox-mediated dehalogenation followed by AQ cleavage by ozonolysis.[18]

This reaction likely follows a reaction pathway similar to that of the previous Cu-catalyzed enantioselective aminoalkylation of alkene with 4-alkyl Hantzsch esters, a $Cu(MeCN)_4PF_6$ catalyst, and a biaryl phosphine oxide ligand (Scheme 5).[12,19] A Cu^I catalyst might first be oxidized by oxime ester **V** via single-electron transfer (SET) to form Cu^{II} and iminyl radical **VI**. **VI** then rearranges to generate alkyl radical **VIII**, which attacks IQ-chelated Cu^{II} alkene complex **II** to form five-membered Cu^{III}-metallacycle **III**. Intramolecular reductive

Scheme 5. Mechanistic Considerations



elimination (RE) of **III** gives β-lactam product **IV** in *anti*-diastereoselectivity and regenerates Cu^I. As a competing pathway, alkyl radical **VIII** can react with IQ-chelated Cu^{II} to form an alkyl-Cu^{III} intermediate **IX**, which gives the N-alkylation side product **X** upon C–N RE. The ligand (L) on Cu complexes **II** and **III** could strongly influence their reactivity. Our control experiments showed that strong coordinating ligands such as OAc and iodide suppress the formation of the β-lactam product. Notably, it was proposed that OBz-facilitated concerted β-elimination of Cu^{III} complex **XI** affords alkylated alkene product **XII** in Fu's system.[9] Interestingly, benzoate anion **VII** is also generated in our system but does not cause β-elimination. We suspect that the OAc or iodide ligand might play a more relevant role in the β-elimination of **III**.

In summary, we have developed a Cu-catalyzed aminoalkylation reaction of unactivated alkenes using cyclobutanone oxime esters as the donor of alkyl radicals and 5-iodo-8-aminoquinoline as the directing auxiliary. Both primary and secondary alkyl groups can be selectively installed at the C_4 position of terminal or *cis*-internal 3-alkenamides in moderate to good yield. This reaction offers a useful method for the diastereoselective synthesis of β-lactams bearing various 4-cyanoalkyl β-substituents. Further studies are needed to better understand and improve the chemoselectivity of this Cu-catalyzed radical-mediated reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01007.

Detailed synthetic procedures, compound characterization, NMR spectra, X-ray crystallographic data, and computational details (PDF)

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Accession Codes

CCDC 2071976 contains 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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