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Article

Enantioselective Alkylamination of Unactivated Alkenes under Copper Catalysis

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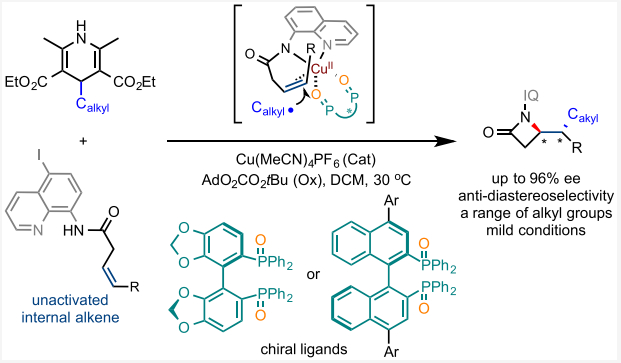
ABSTRACT: An enantioselective addition reaction of various alkyl groups to unactivated internal alkenes under Cu catalysis has been developed. The reaction uses amide-linked aminoquinoline as the directing group, 4-alkyl Hantzsch esters as the donor of alkyl radicals, and rarely used biaryl diphosphine oxide as a chiral ligand. β-lactams featuring two contiguous stereocenters at Cβ and the β substituent can be obtained in good yield with excellent enantioselectivity. Mechanistic studies indicate that a nucleophilic addition of the alkyl radical to Cu^{II}-coordinated alkene is the enantio-determining step.



INTRODUCTION

Catalytic asymmetric functionalization (CAF) of alkenes can streamline the stereoselective construction of complex carbon skeletons.[1] Among these functionalization reactions, the enantioselective addition of alkyl groups is arguably the most valuable as it provides a means to construct alkyl-substituted stereocenters.[2] While considerable progress has been made in the asymmetric functionalization of activated alkenes, the enantioselective transformation of unactivated alkenes, especially via intermolecular reaction, remains challenging. The reported success has been mainly limited to terminal alkenes participating in intramolecular reactions.[3] The enantioselective functionalization of unactivated internal alkenes poses an even greater challenge due to regiocontrol and reactivity issues. Recently, a substrate-directed approach has emerged as an attractive strategy to facilitate the metal-catalyzed enantioselective functionalization of unactivated terminal and internal alkenes.[1f,4] Various directing groups (DG) have been employed to facilitate the enantiodetermining addition of an R_1 group to double bonds via migratory insertion, or nucleometalation, to form an alkylmetal intermediate, which is further functionalized or protonated (Scheme 1A).[5] Recently, Cu-catalyzed radical-mediated processes have emerged as a new means for the enantioselective difunctionalization of unactivated terminal alkenes. Most of these reaction systems involve the initial nonstereoselective trapping of electron-deficient radicals such as CF_3· by alkenes to generate a new alkyl radical, which then reacts with heteroatom-linked DG to form a cyclized product with enantiocontrol.[6,7] Despite these exciting advances, the mode of carbofunctionalization of alkenes is still limited to the addition of aryl, acyl, alkynyl, and special alkyl groups. The enantioselective addition of normal alkyl groups to unactivated alkenes remains challenging. Herein, we report an amide-directed asymmetric difunctionalization of unactivated alkenes via the enantioselective addition of alkyl radicals under Cu catalysis. The reaction uses 4-alkyl Hantzsch esters as the donor of alkyl radicals and the biaryl diphosphine oxide ligand as a chiral ligand. This reaction offers a convenient and efficient method for the asymmetric synthesis of β-substituted β-lactams bearing two contiguous stereocenters.[8]

RESULTS AND DISCUSSION

Over the past few years, the Engle group has demonstrated that the amide-linked bidentate aminoquinoline (AQ or Q) directing group can facilitate the functionalization reactions of unactivated alkenes with a variety of coupling partners under Pd catalysis (Scheme 1B).[9−11] The pathway of these reactions typically involves an AQ-controlled nucleopalladation of alkene to form a kinetically favored palladacycle intermediate, which is then protonated or reacts with suitable electrophiles to give mono- or difunctionalized products. We and the Engle group later showed that some of these carbofunctionalization reactions can proceed in enantioselective fashion using monodentate oxazoline (MOX) ligands.[11] However, asym-

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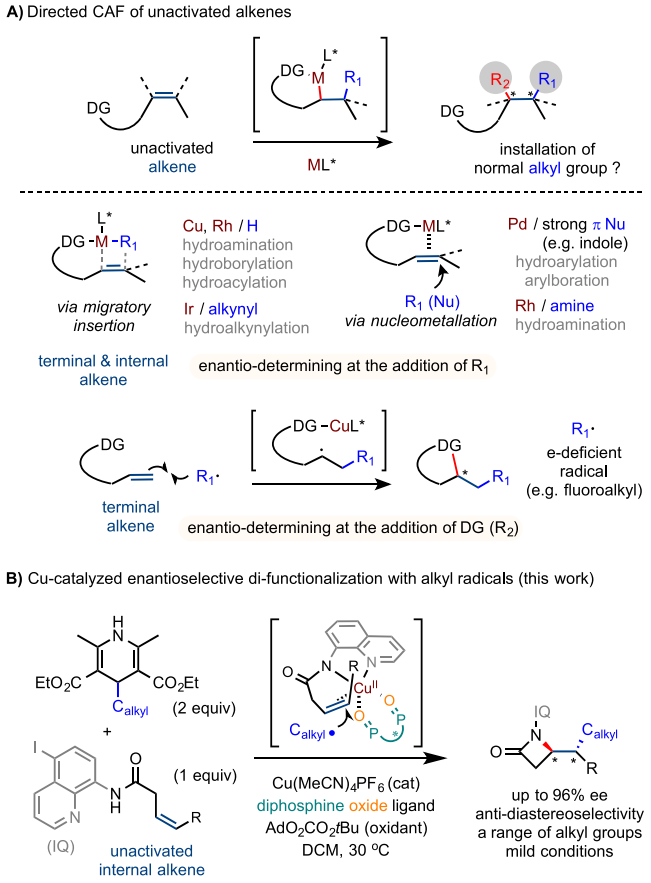
Scheme 1. Directed CAF of Unactivated Alkenes



metric carbofunctionalization is mainly limited to the addition of π nucleophiles such as indoles or enolates. This AQ-directed reaction strategy has also been extended to other transformations under the catalysis of different metals.[12,13] Notably, the Zhao group recently reported an interesting carboamination of alkenes with benzyl radicals under Cu catalysis.[14] It was proposed that benzyl radicals, generated from the in situ hydrogen atom abstraction of methylarene (e.g., toluene), add to alkene to form an AQ-chelated Cu^{III}-metallacycle, which undergoes intramolecular C−N reductive elimination to give a β-lactam product. The reaction required relatively forced conditions using the di-*tert*-butyl peroxide (DTBP, **O1**) oxidant and methylarene as a solvent at 130 °C. Encouraged by the study, we questioned whether we can develop a more generally applicable and even enantioselective version of this reaction under mild operating conditions.

We commenced our study with the model reaction of *N*-quinolyl-*cis*-3-hexenamide (**1**) with 4-alkyl-1,4-dihydropyridines (alkyl-DHP, Hantzsch esters), which recently have emerged as excellent radical donors in various redox catalytic systems (Table 1).[15,16] The reaction of **1** and 2 equiv of Bn-DHP (**2**) in the presence of 10 mol % $Cu(MeCN)_4PF_6$ catalyst, 2 equiv of **O1** oxidant, and 20 mol % MOX in chiral ligand **L1** at 50 °C in 1,2-dichloroethane (DCE) gave the desired product **3** in 12% yield, exclusive *anti*-diastereoselectivity, and promising enantioselectivity (71:29 er) (entry 1). Other oxazoline ligands such as MOXca **L2** and BOX-type ligands gave lower er values and yields. (See the SI for more details.) Interestingly, diphosphine oxide BINAPO **L5** gave significant reactivity and enantio-induction enhancement (52% yield, 82:18 er, entry 2), whereas diphosphine BINAP **L4** gave little **3**. The use of oxidant **O2** gave a slightly higher yield of **3** (entry 3). The installation of an iodine at C_8 of the quinoline auxiliary improved the er of **3** to 92:8 (IQ, entries 4−7).[17] The use of peroxycarbonate oxidant **O4**, recently introduced by Liu,[18] allowed the reaction to take place efficiently at room temperature, forming **3** in higher yield and with a 95:5 er (entries 9−11). Finally, the use of SEGPHOS-based oxide ligand **L7** in dichloromethane (DCM) gave the highest er (entry 19). Product **3** was obtained in 72% isolated yield with 97:3 er using 30 mol % SEGPHOSO (entry 20). As shown in entry 24, reaction with **O4** in the absence of ligand gave a considerable amount of *N*-benzylation side product **4** (~16%) and double-alkylation side product **5** (32%). The use of diphosphine ligands such as **L6** gave results comparable to those of **L7** when the **O4** oxidant was used because they can be quickly oxidized (>95% conversion within 3 h) *in situ* to generate the corresponding oxide ligands. In comparison, only a small amount of oxidation product **L4** or **L6** (~20% in 12 h) was observed when oxidants **O1** and **O2** were used. (See the SI for details.) Monophosphine oxide ligand **L8** gave a racemic product. Cu^{I} catalysts bearing strong coordinating anionic ligands such as halide or acetate provided little reactivity (entries 12 and 13). Cu^{II} catalysts were significantly less effective (entry 17). Notably, the use of the CuOTf catalyst gave the highest yield of **3** but with a slightly decreased er (95:5, entry 21). The addition of 3 equiv of radical trapping reagent butylated hydroxytoluene (BHT) suppressed the formation of **3**, giving benzyl-BHT adduct **6** in 42% yield (entry 25; see the SI for details).

Substrate Scope. With the optimized conditions in hand, we next examined the scope of 4-benzyl Hantzsch esters using the reaction of IQ-coupled *cis*-3-hexenamide **1** (Scheme 2A).[19] Overall, benzyl-DHPs bearing various substituents on the phenyl ring worked well, giving the desired β-lactam products (**8**−**13**) in good to excellent yields, exclusive anti diastereoselectivity, and high enantioselectivity (up to 98:2 er). The absolute stereochemistry of **3** was determined by X-ray crystallography. In comparison with **3**, compound **3′** equipped with an AQ group was obtained in slightly diminished yield and er under the same conditions. In comparison with *cis*-3-hexenamide **1**, the reaction of its trans alkene isomer, ***trans*-1**, gave lactam product **7** in much lower yield (~12%), with excellent diastereoselectivity and slightly diminished enantioselectivity (91:9 er; absolute stereochemistry was not determined) under the same conditions. As shown in Scheme 2B, a variety of *cis*-3-alkenamides bearing different terminal R groups reacted with benzyl-DHPs to give the corresponding β-lactams in good yields and with high er values under the standard conditions. Terminal alkene (**15**), primary alkyl chloride (**16**), and cyclopropyl (**17**) groups were tolerated. The reaction of *cis*-3-phenyl-3-butenamide gave **19**. This chemoselectivity is different from that of many reported Cu-catalyzed reactions in which the alkyl radical tends to attack the outer position of aryl alkenes to form a more stable benzylic radical intermediate. The structure of **19** was confirmed by X-ray crystallography. (See the SI.) The reaction of terminal alkene 3-butenamide with benzyl-DHP gave simple β-lactam product **20** in good yield and with excellent enantioselectivity. The reaction of 3-butenamide with 1-phenylethyl-DHP gave **22** as a 1.1:1 diastereomeric mixture at the benzylic position.

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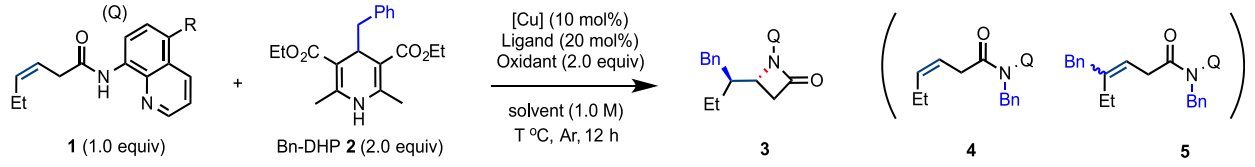
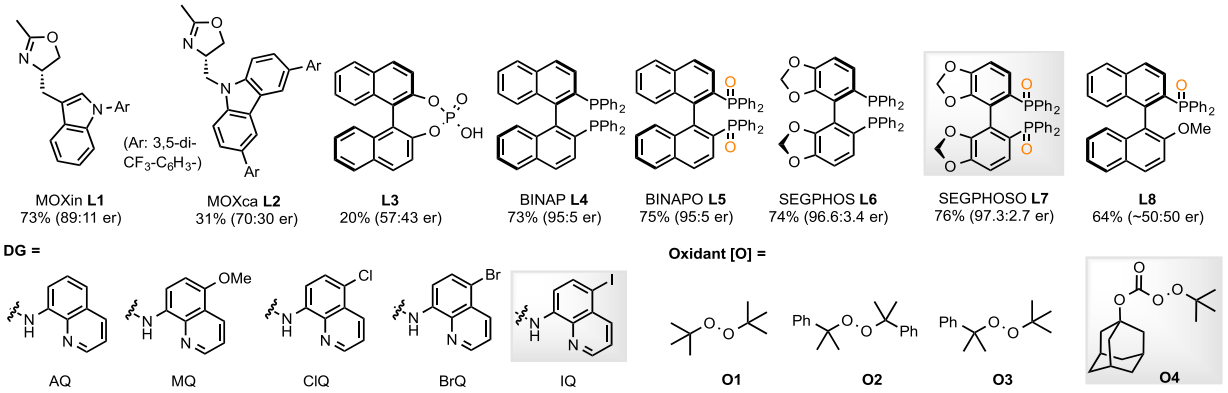
Table 1. Optimization of the Enantioselective Addition of the Benzyl Radical to 1[a]



entry	[Cu]	ligand	oxidant	DG	T/°C	solvent	yield of **3** % (er)[b]
1	$Cu(MeCN)_4PF_6$	**L1**	**O1**	AQ	50	DCE	12 (71:29)[c]
2	$Cu(MeCN)_4PF_6$	**L5**	**O1**	AQ	50	DCE	52 (82:18)
3	$Cu(MeCN)_4PF_6$	**L5**	**O2**	AQ	50	DCE	60 (81:19)
4	$Cu(MeCN)_4PF_6$	**L5**	**O2**	ClQ	50	DCE	48 (91:9)
5	$Cu(MeCN)_4PF_6$	**L5**	**O2**	BrQ	50	DCE	54 (87:13)
6	$Cu(MeCN)_4PF_6$	**L5**	**O2**	MQ	50	DCE	67 (62:38)
7	$Cu(MeCN)_4PF_6$	**L5**	**O2**	IQ	50	DCE	53 (92:8)
8	$Cu(MeCN)_4PF_6$	**L5**	**O3**	IQ	50	DCE	57 (89:11)
9	$Cu(MeCN)_4PF_6$	**L5**	**O4**	IQ	50	DCE	57 (92:8)
10	$Cu(MeCN)_4PF_6$	**L5**	**O4**	IQ	30	DCE	70 (95:5)
11	$Cu(MeCN)_4PF_6$	**L5**	**O4**	IQ	25	DCE	68 (95.5:4.5)
12	CuI	**L5**	**O4**	IQ	30	DCE	trace
13	CuOAc	**L5**	**O4**	IQ	30	DCE	trace
14	CuOTf	**L5**	**O4**	IQ	30	DCE	77 (90:10)
15	$Cu(MeCN)_4BF_4$	**L5**	**O4**	IQ	30	DCE	34 (95:5)
16	$Cu(MeCN)_4OTf$	**L5**	**O4**	IQ	30	DCE	71 (92:8)
17	$Cu(OTf)_2$	**L5**	**O4**	IQ	30	DCE	39 (85:15)
18	$Cu(MeCN)_4PF_6$	**L7**	**O4**	IQ	30	DCE	75 (96.7:3.3)
19	$Cu(MeCN)_4PF_6$	**L7**	**O4**	IQ	30	DCM	76 [66[d]] (97.3:2.7)
20	$Cu(MeCN)_4PF_6$	**L7** (30 mol %)	**O4**	IQ	30	DCM	84 [72[d]] (97.0:3.0)
21	CuOTf	**L7** (30 mol %)	**O4**	IQ	30	DCM	90 [82[d]] (95:5)
22	$Cu(MeCN)_4PF_6$	**L7**	**O4**	IQ	30	MeCN	72 (95:5)
23	$Cu(MeCN)_4PF_6$	**L7**	**O4**	IQ	30	DCE/H_2O (1/1)	57 (93:7)
24	$Cu(MeCN)_4PF_6$	no ligand	**O4**	IQ	30	DCM	50 (50:50)[e]
25	$Cu(MeCN)_4PF_6$	**L7** + BHT (3 equiv)	**O4**	IQ	30	DCM	trace[f]

[a]Yield (NMR) and er of **3** using different chiral **ligands** [**L**] under the conditions listed in entry 19.



[b]All reactions were carried out on a 0.1 mmol scale. Yields were determined by ^{1}H NMR analysis of the reaction mixture after workup using CH_2Br_2 as an internal standard. er was measured by chiral HPLC. [c]~80% yield of **1** recovered. [d]Isolated yield. [e]Along with 16% yield of **4** and 32% yield of **5**. [f]42% yield of benzyl-BHT **6** was formed. See the SI for more results.

As exemplified by **23** in Scheme 3, normal alkyl-DHPs can also react with the *cis*-alkene substrates with excellent er under general conditions **A**. However, a significant amount of the *N*-alkylation side product (such as **4** in Table 1) was formed. A reexamination of the ligands revealed that BINAPO ligands bearing aryl substituents on C4 and C4′ can suppress the undesired *N*-alkylation while maintaining a high er. The aryl groups can be readily installed via Suzuki coupling with the corresponding bromo-BINAPO precursor. (See the SI for details.) The sterics and electronics of the aryl groups had a strong impact on the reactions. **L11** bearing a 3,5-dimethoxylaryl group gave the best results, forming β-lactam **23** in 72% isolated yield and with 95:5 er (conditions **D**). In general, secondary and tertiary alkyl groups (e.g., **24** and **25**) worked well under the optimized conditions with the **L11** ligand. The reactions of primary alkyl groups (e.g., the ethyl group in **27**) remained problematic. The reactions of terminal alkene 3-butenamide with alkyl-DHPs also gave good results (e.g., **28**), whereas the reactions with *trans*-alkenes still proceeded with low yields (<10%).

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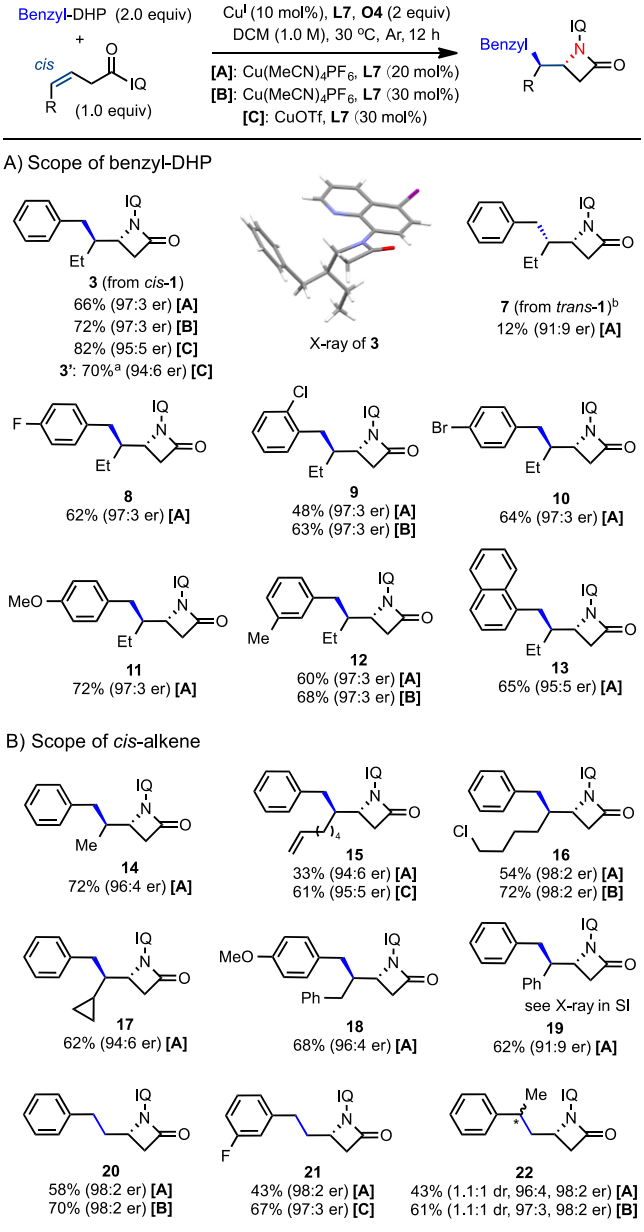
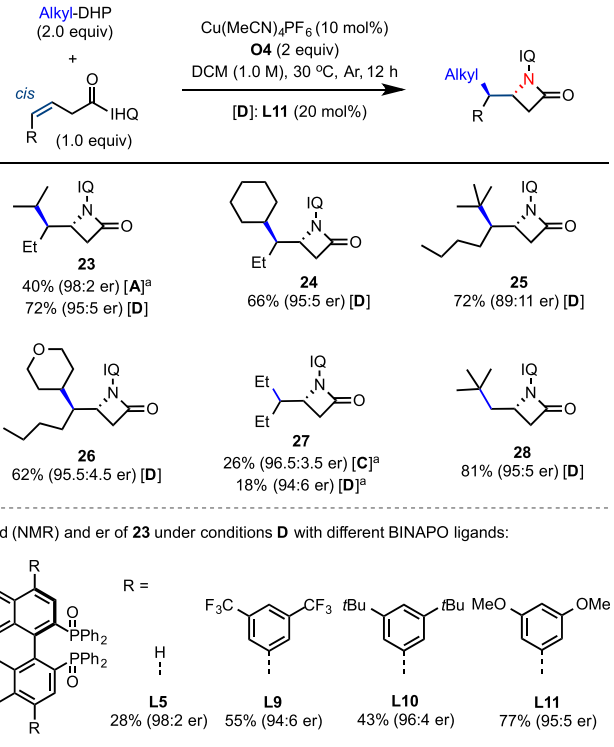
Scheme 2. Reactions of Benzyl-DHPs[a]



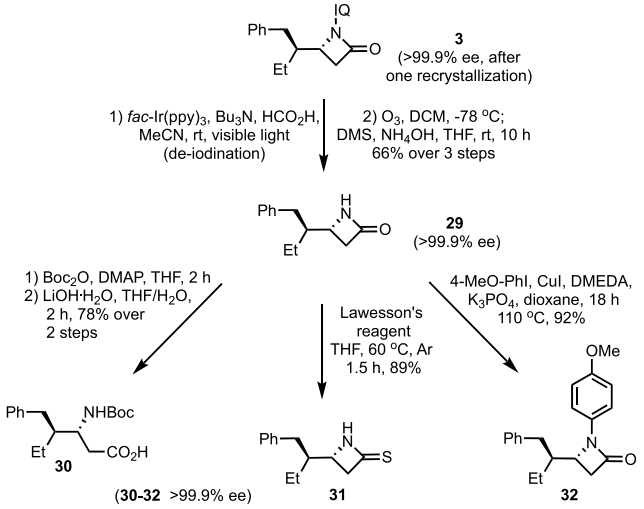
[a]Isolated yields on a 0.1 mmol scale. *cis*-Alkene substrates were used unless otherwise specified. (a) IQ in **3** is replaced with AQ. (b) ~40% yield of SM was recovered along with the formation of a 35% yield of the *N*-alkylation side product.

Scheme 3. Reactions of Alkyl-DHPs[a]



[a]Isolated yields on a 0.1 mmol scale unless otherwise specified. (a) A significant amount of the *N*-alkylation side product (>30%) was formed. See the SI for more results on ligand screening.

Scheme 4. Synthesis Utility



As shown in Scheme 4, product **3** was prepared in 60% yield and with 97:3 er on the gram scale under standard conditions **A**. One recrystallization gave **3** in >99.9% ee. The IQ group of **3** was cleanly removed via a three-step sequence to give **29**: Stephenson's visible-light-mediated dehalogenation followed by Maulide's protocol of AQ cleavage by ozonolysis.[20] Boc activation of the lactam ring of **29** followed by treatment with LiOH gave *β*-amino acid **30**.[21] The treatment of **29** with Lawesson's reagent gave chiral *β*-thiolactam **31**. The Cu-catalyzed *N*-arylation of **29** with aryl iodide gave **32** in high yield. The stereochemical integrity of compounds **30**−**32** was preserved.

Mechanistic Study. On the basis of our experimental results and published studies, we propose a radical-mediated mechanism for this Cu-catalyzed enantioselective difunctionalization of unactivated alkene (Scheme 5A). The Cu^{I} catalyst first undergoes single electron transfer (SET) oxidation with **O4** to give a *t*-butoxy radical and Cu^{II}, which forms a complex with alkene substrate **I** and diphosphine oxide ligand **L***. The *t*-butoxy radical reacts with R-DHP to generate a nucleophilic alkyl radical R·, pyridine **V**, and a *t*-butoxy anion. AQ-chelated Cu^{II}/alkene complex **II** then undergoes a nucleophilic (Wacker-type) addition with R· at the *γ* position, forming five-membered Cu^{III}-metallacycle **III**. Intramolecular reductive elimination (RE) of **III** gives *β*-lactam product **P-anti** in

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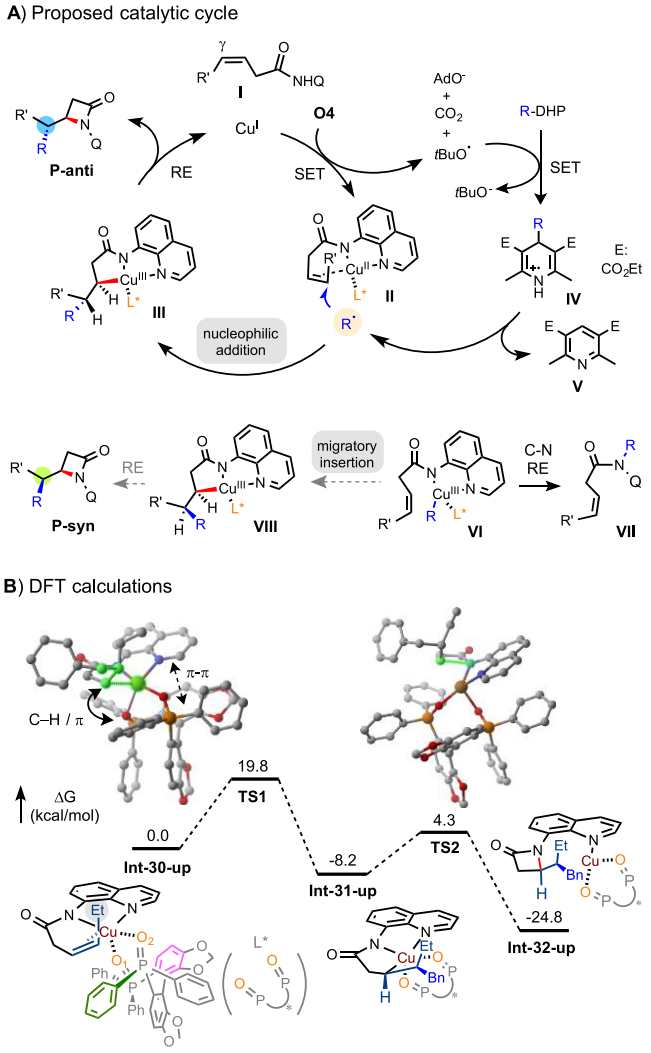
Scheme 5. Mechanistic Studies[a]



[a]DFT calculations were carried out at the PBE0-D3(BJ)/def2-TZVP-SMD(DCM)//B3LYP-D3(BJ)/6-31G*+LANL2DZ level. See the SI for more calculations on enantioselectivity and the *N*-alkylation side reaction.

antidiastereoselectivity and regenerates Cu^{I}. R· can also add to Cu^{II} to form alkyl-Cu^{III} intermediate **VI**, which gives *N*-alkylation product **VII** via RE. As an alternative pathway, the R group of **VI** could undergo migratory insertion with the double bond to form **VIII**, which gives product **P-syn** with syn diastereoselectivity.[22] The stereochemistry of our *β*-lactam products is consistent with a nucleophilic addition pathway.

Density functional theory (DFT) calculations were performed to estimate the energetics and enantioselectivity of the model reaction of **1** and **2** under the control of *R*-**L7** (Scheme 5B).[23] Intermediate **Int-30-up** with the ethyl group pointing up and the O_1 atom of **L7** placed underneath the AQ plane represents the most stable complex of **1**, Cu^{II}, and **L7**.[24] Attack by the benzyl radical at the *γ* position of **Int-30-up** via transition state **TS1** proceeds with an energy barrier of 19.8 kcal/mol to give metallacycle intermediate **Int-31-up**. Noncovalent interaction analysis of **TS1** reveals attractive *π*−*π* interactions between AQ and one of the benzodioxole groups of **L7** (marked in purple) and C−H/*π* interactions between *β* alkenyl C−H and the phenyl group of **L7** (marked in green). C−N RE of **Int-31-up** proceeds via **TS2** with a small energy barrier of 4.3 kcal/mol to give *β*-lactam **Int-32-up**, which matches the stereochemistry of the experimental results. In comparison with **Int-30-up**, corresponding Cu^{II}/alkene complex **Int-30-down** with the ethyl group pointing down is less stable and requires a higher energy barrier for the subsequent addition of the benzyl radical, giving minor stereoisomer **Int-30-down** (comparative analyses of Cu/alkene complexes with four different stereoarrangements of alkene and the **L7** ligand given in the SI).[25] Addition of the benzyl radical is the enantio-determining step of the reaction sequence.

CONCLUSIONS

We have developed an unprecedented enantioselective addition reaction of alkyl radicals to unactivated internal alkenes under Cu catalysis using the combination of the aminoquinoline directing group and the biaryl diphosphine oxide chiral ligand. This reaction offers an efficient method for the asymmetric synthesis of complex *β*-lactams that are difficult to access by other methods. Unlike most of the previous Cu-catalyzed asymmetric additions of radicals to terminal alkenes, Cu is intimately involved in the enantio-determining addition of radical species to the internal alkene, enabling stereocontrol at both carbons of the alkene to establish contiguous stereogenic centers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12333.

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

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checkCIF/PLATON report for datablock r20200703b (PDF)

Crystallographic data of compound **3** (CIF)

Crystallographic data of compound **19** (CIF)

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Notes

The authors declare no competing financial interest.

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V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A.; Peralta, Jr., J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016. Geometries were optimized at the B3LYP-D3(BJ)/6-31G*+LANL2DZ(Cu) level of theory in the gas phase. Single-point energies were calculated at the PBE0-D3(BJ)/def2-TZVP level with the SMD solvation model in DCM. See the SI for computational details.

(24) The sterics of *trans*-alkene might prevent the fitting of the double bond into the chiral pockets of the Cu catalyst.

(25) In comparison with the other transition states with different stereochemical arrangements, the attack of the benzyl radical via **TS1** encounters less steric hindrance. See the SI for details.

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