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Communication

Quinim: A New Ligand Scaffold Enables Nickel-Catalyzed Enantioselective Synthesis of α-Alkylated γ-Lactam

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ABSTRACT: Herein, we report a nickel-catalyzed reductive cross-coupling reaction of easily accessible 3-butenyl carbamoyl chloride with primary alkyl iodide to access the chiral α-alkylated pyrrolidinone with broad substrate scope and high enantiomeric excess. The current art of synthesis still remains challenging on the enantioselective α-monoalkylation of pyrrolidinones. The newly designed chiral 8-quinoline imidazoline ligand (Quinim) is crucial for maintaining the reactivity and enantioselectivity to ensure the reductive cyclization of monosubstituted alkenes for unprecedented synthesis of chiral non-aromatic heterocycles.

The γ-lactam represents one of the most significant and ubiquitous structural motifs in the framework of numerous biologically active natural products and pharmaceuticals.[1] Thus, tremendous efforts have been devoted to the efficient construction of chiral γ-lactam in organic and enzymatic synthesis.[2,3] Particularly, chiral α-alkylated pyrrolidinone is a vital class of scaffold that exhibits biological reactivity (Figure 1).[4] However, the enantioselective α-monoalkylation

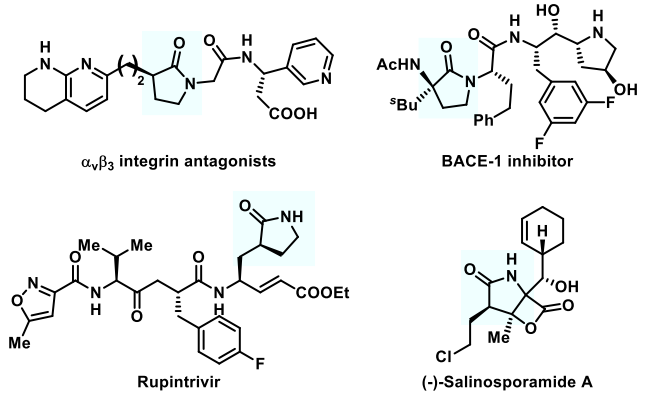
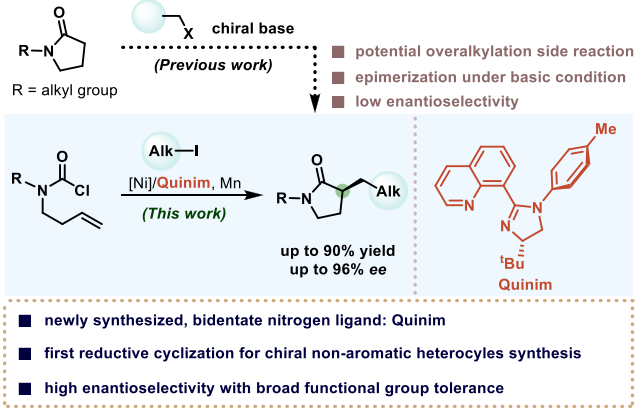


Figure 1. Examples of pharmaceuticals and biologically active compounds bearing chiral α-alkylated pyrrolidinone.

of easily accessible γ-lactam still remains a challenge due to the potential overalkylation side reaction as well as epimerization under basic condition; even a stoichiometric chiral base could only lead to low enantioselectivity and yield (Scheme 1).[5] The major approach in medicinal chemistry for the chiral α-alkylated pyrrolidinone synthesis still mainly relies on the introduction the chirality via the α-alkylation of Evan's auxiliary, followed by multiple synthetic manipulations to form the pyrrolidinone ring.[4a−c] Only recently, a few asymmetric catalytic methodologies have been employed for the synthesis of α-alkylated pyrrolidinone, including the asymmetric hydrogenation of cyclic aryl-substituted enamides developed by the Zhang and Ding groups independently to

Scheme 1. Approaches for Asymmetric Synthesis of α-Alkylated Pyrrolidinones



synthesize the chiral α-benzyl pyrrolidinone,[6] and asymmetric hydrocarbamoylation of alkene-tethered formamides with the incorporation of a methyl group adjacent to the lactam group developed by Cramer and co-workers.[7] Despite these advances, it is still highly desirable to achieve the chiral α-alkylated pyrrolidinone synthesis in asymmetric catalysis, introducing the simple and unactivated alkyl group with broad functional group tolerance.

Transition-metal-catalyzed enantioselective difunctionalization of alkene has emerged as a useful synthetic tool for the simultaneous introduction of two functionalities across the double bond, alongside increasing molecular complexity.[8,9] Ni-catalyzed asymmetric reductive difunctionalization of alkenes is

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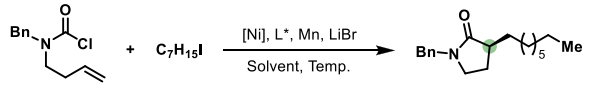
especially of great research interest, as it circumvents the use of preformed organometallic nucleophiles.[10−14] Most two-component enantioselective reductive cross-coupling protocols are initiated from the intramolecular cyclization of aryl (pseudo)-halide-tethered 1,1-disubstituted alkenes to generate a chiral quaternary center with the formation of a benzo-fused ring system.[10] However, synthesis of simple chiral non-aromatic heterocycles, such as pyrrolidinones, using asymmetric reductive cross-coupling still remains elusive, likely due to the difficulty in the stereoselective radical migratory insertion.[11a,b] Based on our continuous research interest in Ni-catalyzed carbonylations,[15] we are intrigued that homoallylic carbamoyl chloride would be an appropriate precursor to access the chiral pyrrolidinone synthesis. Carbamoyl chloride could be synthesized from easily available secondary amines and is well recognized as a versatile building block for the synthesis of nitrogen-containing heterocycles.[16] Since the seminal work by Grigg[17] and Takemoto,[18] transition-metal-catalyzed cyclization of 1,1-disubstituted alkene-tethered carbamoyl chloride has offered a straightforward route to construct oxindole scaffolds.[19] More recently, the incorporation of a quaternary stereogenic center in oxindole derivatives has been realized independently by the Lautens[20] and Wang groups.[10i,j] To the best of our knowledge, the enantioselective cyclization of monosubstituted alkene-tethered carbamoyl chloride for the formation of non-aromatic heterocycles has not been achieved. Herein, we disclose a newly developed 8-quinoline imidazoline (Quinim) ligand-enabled, Ni-catalyzed enantioselective reductive cross-coupling of a monosubstituted alkene-tethered carbamoyl chloride with unactivated primary alkyl iodide to access the non-aromatic heterocycle, α-monoalkylated pyrrolidinone; the non-basic condition allows the formation of the tertiary chiral center without the erosion of enantiomeric excess (*ee*).

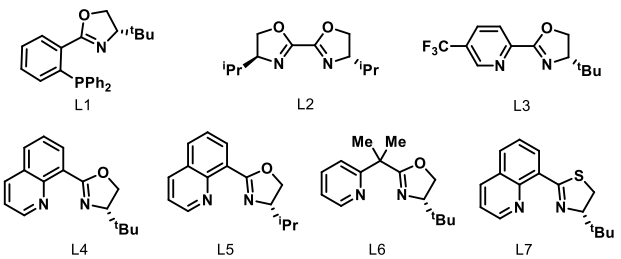
At the outset of our investigation, we selected carbamoyl chloride **1a** as the model substrate with primary alkyl iodide **2a** as the coupling component. The chiral ligand screening was performed in *N*-methyl-2-pyrrolidone (NMP) at 30 °C with $Ni(ClO_4)_2{\cdot}6H_2O$ as catalyst and Mn as reducing reagent. Employing the common chiral ligand utilized in Ni-catalyzed reductive cross-coupling achieved limited success (Table 1, entries 1−3).[21] After many trials, we were gratified to realize that the 8-Quinox **L4**, originally developed by Zhou and co-workers decades ago,[22] elevated both reaction yield and enantiomer ratio (e.r.), whereas the efficiency dramatically dropped with **L5**, which indicated the importance of a *tert*-butyl group in oxazoline (entries 4 and 5). This less-common six-membered chelation model of the chiral ligand with nickel catalyst encouraged us to investigate the ligand effect. The ligand **L6**, which resulted from removing the benzene ring from **L4**, completely failed to afford the desired product, demonstrating that the configuration of 8-Quinox is crucial for this reductive cross-coupling (entry 6). To our delight, when the oxazoline moiety was changed to the more electron-rich chiral imidazoline backbone at the 8-position of quinoline, the Quinim **L8** provided the desired product **3a** in 92:8 e.r., albeit with low yield (entry 8).[23] Both yield and e.r. increased when the reaction was performed at 0 °C (entry 9). Next, we evaluated how substitution on the nitrogen atom in the imidazoline group would alter both electronic and steric effects (entries 10−16). It was found that the electronically neutral aromatic ring of aniline provided the best results (entries 10 and 11), while both an electron-rich 4-methoxyl group (**L11**) and an electron-deficient 4-trifluoromethyl group (**L12**) or the 3,5-ditrifluoromethyl group (**L13**) on the arenes lowered the e.r. Either the introduction of the methyl groups at the *ortho*-position on the aromatic ring (**L14**) or the use of a cyclohexyl group (**L15**) is detrimental to the reaction. Next, replacing NMP with dimethylformamide (DMF) improved the overall reaction efficiency, regarding both yield and enantioselectivity (entry 17). Finally, we could further enhance the yield by employing $Ni(cod)_2$ as catalyst, whereupon the desired γ-

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

Entry	Ligand	Catalyst	Solvent	Temp. (°C)	**3a** (%)[b]	e.r.[c]
1	L1	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	0	-
2	L2	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	12	56:44
3	L3	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	33	68:32
4	L4	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	54	85:15
5	L5	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	17	51:49
6	L6	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	0	-
7	L7	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	0	-
8	L8	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	30	30	92:8
9	L8	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	55	96:4
10	L9	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	39	95:5
11	L10	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	46	96:4
12	L11	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	21	84:16
13	L12	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	36	91:9
14	L13	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	39	84:16
15	L14	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	9	96:4
16	L15	$Ni(ClO_4)_2{\cdot}6H_2O$	NMP	0	12	70:30
17	L8	$Ni(ClO_4)_2{\cdot}6H_2O$	DMF	0	64	97:3
18[d]	**L8**	**$Ni(cod)_2$**	**DMF**	**0**	**92 (86)**	**97:3**
19[d,e]	L8	$Ni(cod)_2$	DMF	0	0	-
20[d,f]	L8	$Ni(cod)_2$	DMF	0	16	83.5:16.5



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 equiv., 0.6 mmol), [Ni] (15 mol%, 0.03 mmol), ligand (22 mol%, 0.044 mmol), Mn (4.0 equiv., 0.8 mmol), LiBr (1.0 equiv., 0.2 mmol), solvent (1 mL) under the indicated temperature for 48 h. [b]Corrected GC yield. [c]Determined by HPLC analysis. [d]$Ni(cod)_2$ (15 mol%, 0.03 mmol); **L8** (18 mol%, 0.036 mmol), 48 h, isolated yield in parentheses. [e]$^nC_7H_{15}Br$ (3.0 equiv) was used instead of **2a**. [f]Zn (4.0 equiv) was used instead of Mn.

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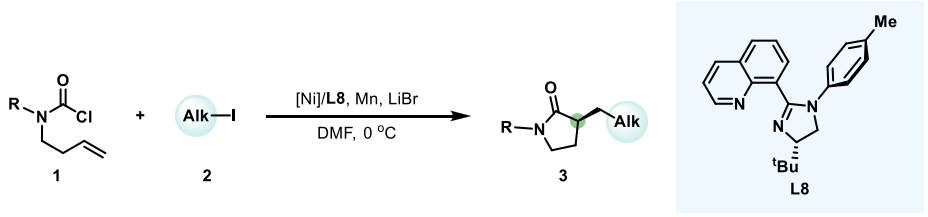
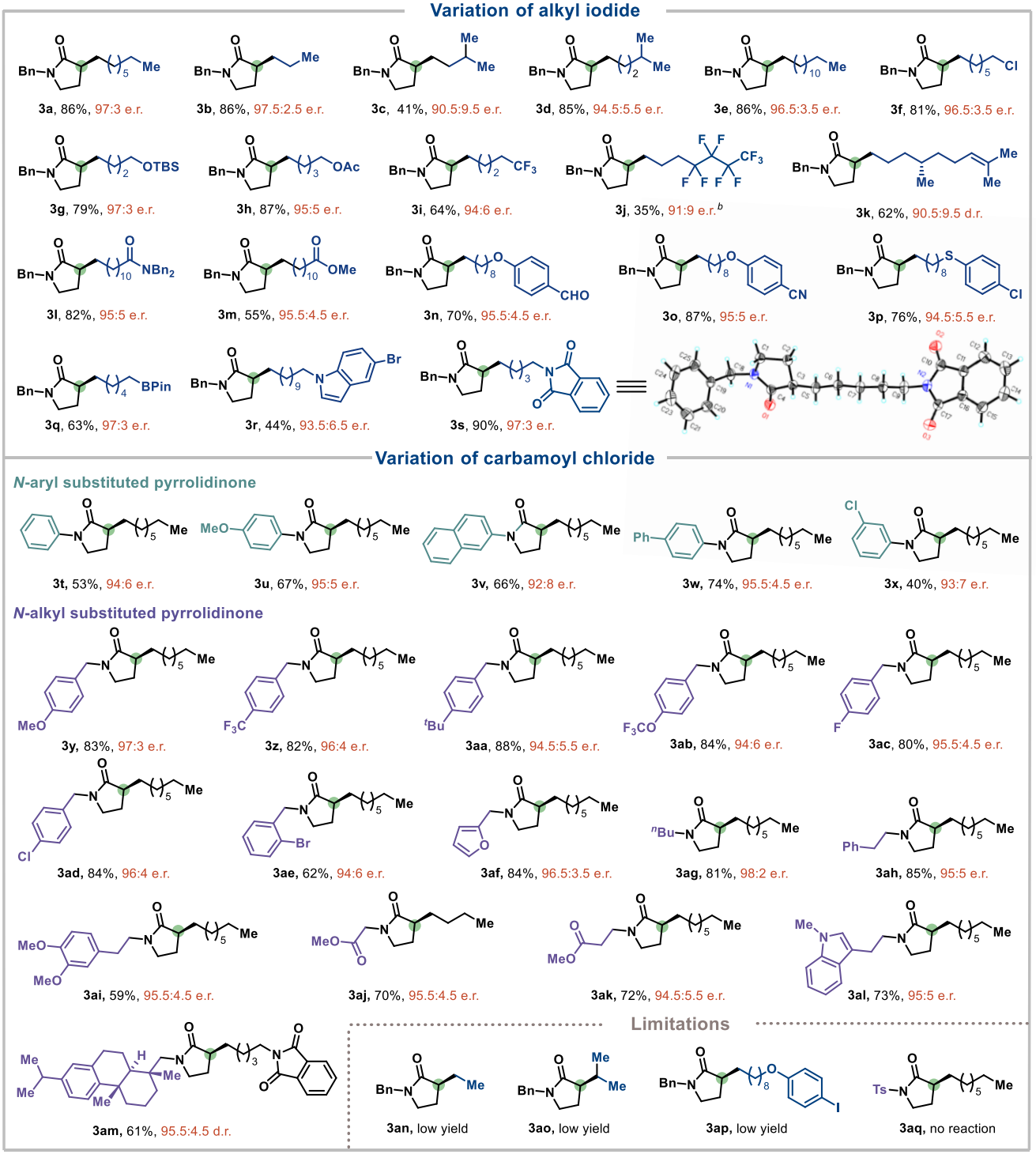
Scheme 2. Substrate Scope of Ni-Catalyzed Enantioselective Carbamoyl-Alkylation of Unactivated Alkenes[a]





[a]Reaction conditions: **1** (1.0 equiv), **2** (3.0 equiv), $Ni(cod)_2$ (15 mol%), **L8** (18 mol%), Mn (4.0 equiv), LiBr (1.0 equiv), DMF (0.2 M), 0 °C for 35−107 h. [b]5 °C

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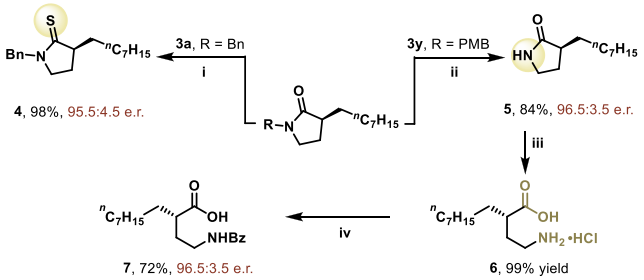
lactam **3a** was obtained in 86% isolated yield with 97:3 e.r. (entry 18). The current protocol was not suitable for primary alkyl bromide, in which case the starting material completely decomposed (entry 19). The reaction efficiency dramatically dropped when zinc powder was employed as the reductant (entry 20).

With the optimized conditions in hand, we investigated the substrate scope of this Ni-catalyzed reductive coupling of homoallylic carbamoyl chloride with alkyl iodide (Scheme 2). It was found that a variety of simple primary alkyl iodides were tolerated; ethyl iodide was also compatible with this protocol (**3b**). It should be noted that yield and enantioselectivity dropped with the introduction of a steric group near the bond-forming center. An isobutyl group could be incorporated into the reaction in 41% isolated yield and 90.5:9.5 e.r. (**3c**), while the product **3d** was obtained in 85% isolated yield and 94.5:5.5 e.r. when isopentyl iodide was employed as the coupling component. Next, we examined the functional group tolerance of alkyl electrophiles. Gratifyingly, alkyl iodides bearing chloride (**3f**), protected ethers (-OTBS for **3g**, -OAc for **3h**), and an internal alkene (**3k**) were obtained with high e.r. Trifluoride- and perfluoride-substituted alkyl electrophiles were also compatible, albeit with lower e.r. (**3i**, **3j**). Additionally, various carbonyl functional groups, including amide (**3l**), ester (**3m**), aldehyde (**3n**), and nitrile (**3o**), were all tolerated under this reductive condition with good e.r. The Ni/**L8** catalyst could selectively react with the alkyl iodide in the presence of the aryl chloride and heteroaryl bromide, with the desired products **3p** and **3r** feasible for further transformation. The success of the BPin functionality highlighted the high selectivity of this reductive condition, and the product **3q** could be further derivatized via C−B bond transformations. Finally, the phthalimide-containing pyrrolidinone **3s** was obtained in 90% isolated yield with high e.r., and the absolute configuration was assigned as *S* configuration, unambiguously confirmed by X-ray diffraction. To our delight, aryl-substituted homoallylic carbamoyl chlorides were tolerated under the standard conditions, providing expedient access to *N*-arylated pyrrolidinones (**3t**−**3x**). The enantioselectivity was high when an electron-donating group was employed (**3u**), while the yield declined when a chloride group was employed in the reaction (**3x**). We next turned our attention to probe the effect of substitution on the homoallylic carbamoyl chloride. It was found that various substituted benzylic groups on the nitrogen atom were compatible, providing a wide scope of functionalized pyrrolidinones (**3y**−**3ae**). Noteworthy was the tolerance of the *ortho*-bromide benzylic *N*-substituted product (**3ae**), allowing further potential derivatization. The presence of heterocyclic rings including furan (**3af**) and indole (**3al**) tolerated the standard conditions with high yield and e.r. Moreover, the simple alkyl-substituted carbamoyl chlorides all proceeded well with high e.r. (**3ag**−**3ai**), even including a complex natural product derivative (**3am**). Notably, both α-amino ester and β-amino ester derivatives can be applied in the current protocol (**3aj**, **3ak**). It should be noted that the γ-lactam **3aj** was prepared by Bristol-Myers Squibb via six synthetic steps.[24] When active MeI (**3an**), secondary ^{i}PrI (**3ao**), and aryl iodide (**3ap**) were employed as the coupling components, the desired product was obtained in low yield. The tosylate-protected carbamoyl chloride (**3aq**) did not work with this Ni/Quinim catalyst, presumably due to the relative slow migratory insertion of the electronic-deficient carbamoyl nickel intermediate.

To further demonstrate the potential synthetic utility of this asymmetric protocol in the construction of valuable skeletons, we performed diverse transformations with the chiral γ-lactam products (Scheme 3). The thioamide **4** could be obtained in

Scheme 3. Derivatization of γ-Lactam[a]



[a]Conditions: (i) 0.5 equiv Lawesson's reagent, **3a**, toluene, 80 °C, 6 h; (ii) 5.0 equiv CAN, **3y**, MeCN/H_2O (5/1), 0 °C, 1 h; (iii) 6 N HCl, 100 °C for 12 h; (iv) 3.0 equiv K_2CO_3, 1.3 equiv PhCOCl, MeCN, 45 °C, 12 h.

98% yield by treatment with Lawesson's reagent. Cleavage of the *p*-methoxybenzyl (PMB) group from **3y** by treatment with ceric ammonium nitrate (CAN) provides **5** in high yield and excellent e.r. retention. Hydrolysis of **5** affords a non-natural γ-amino acid derivative while maintaining the enantiopurity.

We performed preliminary mechanistic studies to shed light on the reaction mechanism (Scheme 4): a stoichiometric experiment was carried out in the absence of alkyl iodide. When 1.0 equiv of $Ni(ClO_4)_2{\cdot}6H_2O$ and 1.0 equiv of Mn powder were employed in the reaction, the 2-methylpyrrolidinone **8** was obtained in 41% isolated yield with 97.5:2.5 e.r., which indicates that the enantioselectivity-determining step (EDS) is the intramolecular migratory insertion of the carbamoyl nickel intermediate into the alkene (Scheme 4a). When 6-iodohex-1-ene was employed as the coupling component, the γ-lactam was obtained as a mixture of **9** and **10** (Scheme 4b). The formation of **10** revealed that the cyclized alkyl radical species might be formed by the single electron transfer (SET) pathway of 6-iodohex-1-ene with the nickel intermediate, followed by intramolecular radical cyclization and then the subsequent coupling to form the cyclized product.[10j,25] The addition of TEMPO (1.0 equiv) completely inhibited the reductive cross-couplings.[26] Therefore, we propose the tentative mechanism in Scheme 4c:[10j] the low-valent nickel undergoes oxidative addition with homoallylic carbamoyl chloride, followed by intramolecular migratory insertion to furnish the alkyl-nickel intermediate **C**, which proceeds with Mn reduction to generate the intermediate **D**. The alkyl iodide reacts with **D** via a SET pathway to form the intermediate **F**, which subsequently furnishes the desired products **3** following reductive elimination.

In conclusion, we have developed a Ni-catalyzed cyclization of carbamoyl chloride with unactivated alkyl iodide to afford the tertiary α-alkylated pyrrolidinone with broad substrate scope in high *ee*. This protocol represents an unprecedented synthesis of chiral non-aromatic heterocycles via an enantioselective Ni-catalyzed reductive cross-coupling strategy. The newly synthesized nitrogen-containing bidentate 8-quinoline imazaloline ligand is the key feature for this transformation, enabling both high reactivity and enantioselectivity. The

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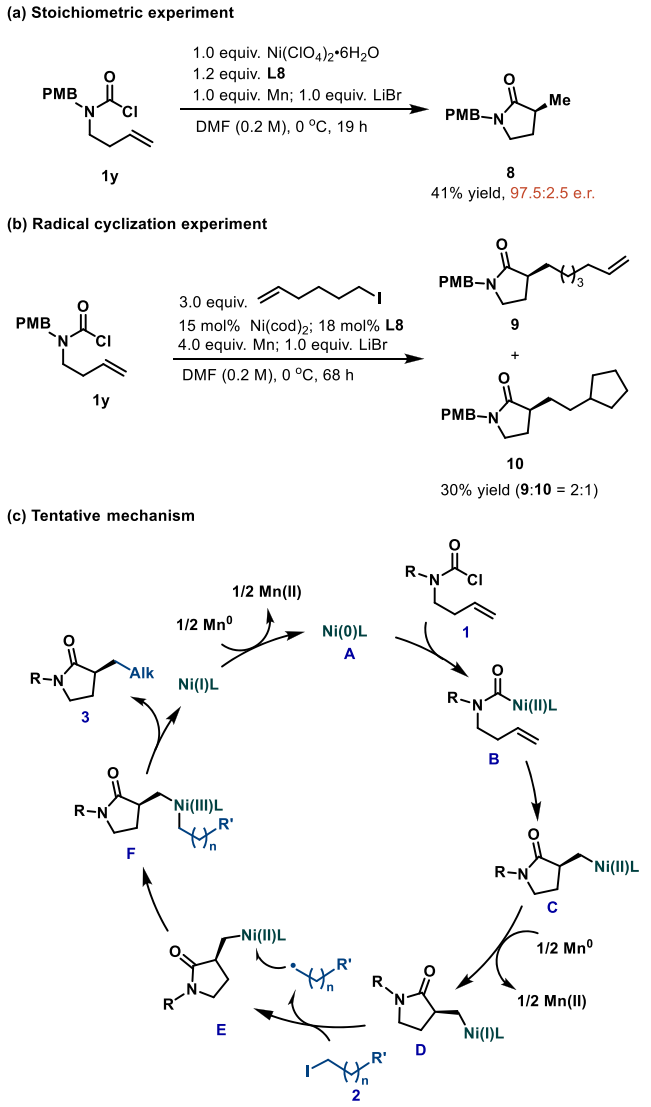
Scheme 4. Plausible Mechanism



investigation of detailed mechanism via theoretical studies and further application of the Quinim ligand in other asymmetric syntheses is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c07126.

Experimental procedures; spectroscopic data for all new compounds including ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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