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Pd-Catalyzed Asymmetric Acyl-Carbamoylation of an Alkene to Construct an α-Quaternary Chiral Cycloketone

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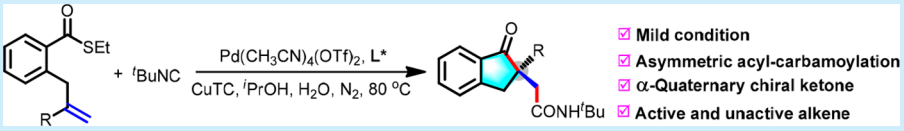
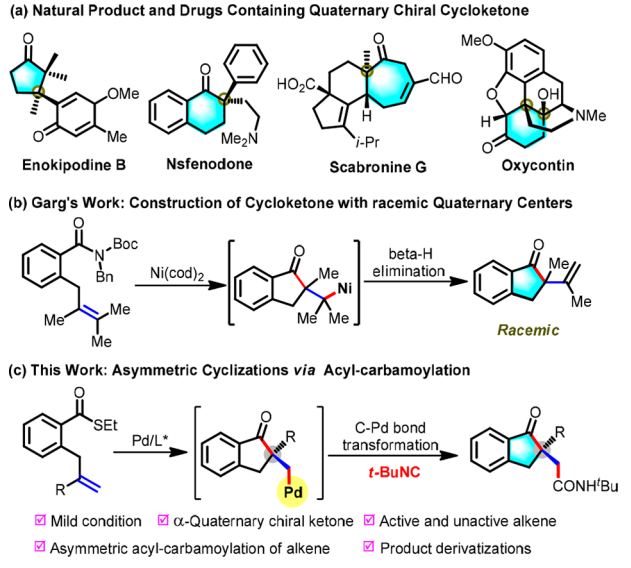
Cite This: https://doi.org/10.1021/acs.orglett.1c02093 Read Online



ABSTRACT: Herein, we report the palladium-catalyzed asymmetric acyl-carbamoylation of an alkene by employing thioesters as the acyl electrophiles and *t*-BuNC as the carbamoyl reagent, affording an α-quaternary chiral cycloketone in synthetically useful yields with excellent enantioselectivity. The reaction proceeded via asymmetric 1,2-migratory insertions of acyl-Pd into alkenes and subsequent migratory insertion of isocyanides into C(sp^3)−Pd^{II}. The product could be diversified to some valuable skeletons with retention of enantiopurity, demonstrating the synthetic utility of this protocol.

Cycloketones with chiral all-carbon quaternary centers are prevalent in natural products and pharmaceuticals (Scheme 1a).[1] Much effort has been devoted to the search for new synthetic methodologies to construct these important structural motifs.[2] Due to the inherent congested nature, the construction of all-carbon quaternary stereocenters represents a formidable challenge. Since the pioneering works by Shibasaki and Overmann in 1989, asymmetric Heck-type carbometalation using aryl halides as electrophiles has been widely employed to install quaternary chiral stereocenters.[3] However, asymmetric Heck-type acyl-metalation using acyl electrophiles to construct α-quaternary chiral cycloketones is rarely reported.[4,5] In 2017, Garg first demonstrated the Ni-catalyzed intramolecular Heck acyl-metalation of an alkene with an amide to introduce the quaternary stereocenters (Scheme 1b).[6] By employing benzoic amide, methyl ester, anhydrides, and acyl chloride as the acyl electrophile, Stanley, Newman, Stambuli, and Chu achieved success in Ni- or Pd-catalyzed acyl-metalation of alkene.[7] Despite these successful examples, migratory insertions of acyl-metal to alkenes often proceed in a racemic fashion.

Scheme 1. Construction of Chiral Quaternary Centers



Compared to other carboxylic acid derivatives, thioesters are active and bench-stable. Thioesters could facilely generate the acyl-metal intermediates via oxidative addition of a C(O)−S bond with low-valent metals, enabling thioester to be employed as the acylation reagent in organic synthesis.[8] For example, palladium-catalyzed cross-coupling of thioester with organometallic reagents has been widely applied to synthesize ketones.[9] Gu elegantly realized the Catellani-type thiolation−acylation of aryl halides with thioester.[10] In 2013, Du Bois and co-workers reported an impressive intramolecular thioester-olefin cross-coupling, forming the cyclic ketone structure with prochiral alkenes.[11] Inspired by previous works,[6−8,11] we speculated about the oxidative addition of thioester with Pd(0) and subsequent asymmetric migratory insertions of acyl-metal into alkenes could afford the α-quaternary chiral ketones with the generation of C(sp^3)−Pd^{II}, which could be further

Received: June 22, 2021

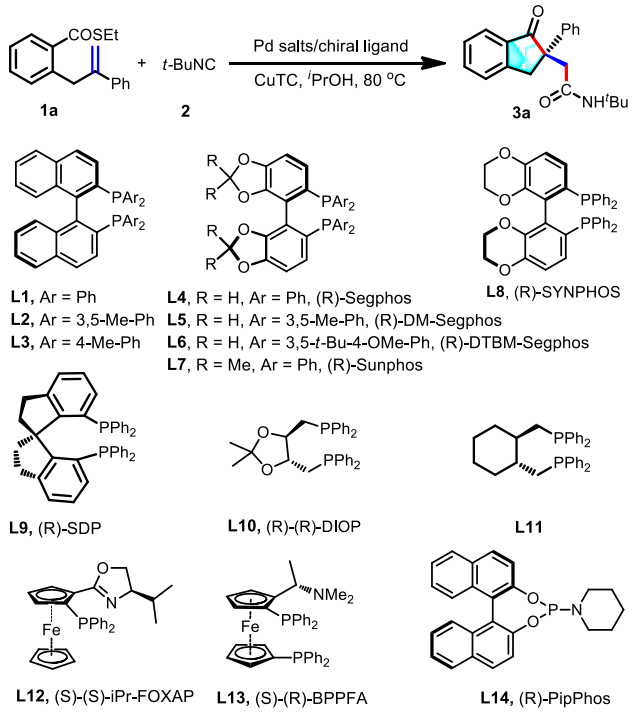
https://doi.org/10.1021/acs.orglett.1c02093
Org. Lett. XXXX, XXX, XXX−XXX

transformed into a variety of functional groups via cross-coupling reaction. Herein, we report the palladium-catalyzed asymmetric acyl-carbamoylation of alkene by employing thioester as the acyl electrophile and *t*-BuNC as the terminating reagent, affording the synthetically important indanone motif bearing a chiral quaternary center (Scheme 1c). It is worth noting that Wang recently reported an elegant nickel/photo-co-catalyzed enantioselective acyl-carbamoylation of alkenes with carbamoyl chloride and aldehydes.[5d]

Isocyanides are isoelectronic with CO and often serve as an appealing carbamoyl source via palladium-catalyzed imidoylation process.[12] Recently, palladium-catalyzed enantioselective imidoylations with isocyanides were achieved by You and Zhu.[13] Thus, we commenced our investigations by employing thioester **1a** and *t*-BuNC **2** as the model substrate (Table 1). However, after the preliminary screening of reaction conditions (see the Supporting Information), we obtained indanone product **3a** in 10% yield with 61% ee in the presence of $PdCl_2$ (10 mol %), (*R*)-BINAP (20 mol %), and CuTC (2.2 equiv) in ^{i}PrOH (entry 1). Interestingly, ^{i}PrOH is the only effective solvent in the reaction, which may act as an agent for the reduction of Pd(II) to Pd(0). The low yield and ee value may be attributed to (1) the congested nature of the quaternary stereocenters[1] and (2) the strong coordinating ability of isocyanide with a palladium catalyst, which may outcompete the chiral ligands.[12,13] To improve the yield and enantioselectivity, we turned our attention to the screening of various ligands. Utilization of modified BINAP ligands **L2** and **L3** slightly improved the yield to 18% with moderate enantioselectivity (entries 2 and 3, respectively). Compared with BINAP (dihedral angle of 73.49°), a biaryl-backbone bisphosphine ligand has a narrower dihedral angle, which may be beneficial for improving the enantioselectivity by strengthening the interaction between the ligand and the substrate.[14] To our delight, (*R*)-SEGPHOS **L4**, developed by Saito,[15] improved the yield to 52% with 91% ee (entry 4). (*R*)-DM-SEGPHOS **L5** was also effective, albeit with lower enantioselectivity (entry 5). However, when (*R*)-SEGPHOS with bulkier derivatives **L6** was employed, no desired product was formed (entry 6). SunPhos **L7** gave the product in 44% yield with 70% ee, while (*R*)-SYNPHOS **L8** afforded a 37% yield with 86% ee (entries 7 and 8, respectively). Spiro phosphine ligand SDP (*R*)-**L9** and (*R*)-DIOP **L10** impeded the reaction (entries 9 and 10, respectively). **L11** as the ligand gave the product in low yield and poor enantioselectivities (entry 11). Bidentate N and P ligands **L12** and **L13** and monodentate ligands **L14** were also screened, and no desired product was detected (entries 12−14, respectively). Further optimization showed that Pd-$(MeCN)_4(OTf)_2$ could slightly improve the yield to 56% (entries 15 and 16). Notably, the addition of H_2O could facilitate the formation of an amide product involving hydrolysis of the imidoyl palladium(II) intermediate, improving the yield to 72% with 90% ee (entry 17).[16] Although acyl-metal species often suffer CO extrusion, no decarbonylation product was detected during the optimization process.[17] Other isocyanides were also tested under the standard reaction conditions; however, no better results were obtained (see the Supporting Information).

Having the optimal reaction conditions and the ligand in hand, we subsequently explored the substrate scope of this asymmetric acyl-carbamoylation reaction. As shown in Scheme 2, substrates bearing electron-donating methyl, methoxyl, and electron-withdrawing fluoro and chloro groups at positions 3−5 of the thioester fragment underwent the domino acyl-carbamoylation efficiently, affording indanone derivatives **3a**−**3k** in 40−72% yields and high ee values. The absolute configuration of **3a** was determined by X-ray structural analysis. With 5 mol % palladium catalyst, chloro and bromo groups could be tolerated, leaving a handle for further structural elaborations (**3f** and **3k**). Then we screened the scope of aryl groups on the vinyl moiety (R group). A wide array of substituents (F, Cl, Br, Me, ^{i}Bu, ^{t}Bu, OMe, and CF_3) at positions 3 and 4 could furnish desired products **3l**−**3u** in 51−67% yields. In contrast, when the fluoro group at position

Table 1. Optimization of the Reaction Conditions[a]



entry	L	Pd salt	yield (%)[b]	ee (%)[c]
1	**L1**	$PdCl_2$	10	61
2	**L2**	$PdCl_2$	18	43
3	**L3**	$PdCl_2$	18	66
4	**L4**	$PdCl_2$	52	91
5	**L5**	$PdCl_2$	53	81
6	**L6**	$PdCl_2$	ND	
7	**L7**	$PdCl_2$	44	70
8	**L8**	$PdCl_2$	37	86
9	**L9**	$PdCl_2$	ND	
10	**L10**	$PdCl_2$	ND	
11	**L11**	$PdCl_2$	8	11
12	**L12**	$PdCl_2$	ND	
13	**L13**	$PdCl_2$	ND	
14	**L14**	$PdCl_2$	ND	
15	**L4**	$Pd(OAc)_2$	38	
16	**L4**	$Pd(MeCN)_4(OTf)_2$	56	91
17[d]	**L4**	$Pd(MeCN)_4(OTf)_2$	72 (68)[e]	90

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), Pd salt (10 mol %), ligand (20 mol %), CuTC (2.2 equiv), 80 °C, *i*-PrOH (2 mL). [b]The yield was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]The ee values were determined by HPLC analysis. [d]With Pd-$(CH_3CN)_4(OTf)_2$ (8 mol %), H_2O (20 equiv), CuTC [copper(I) thiophene-2-carboxylate]. [e]Isolated yield in parentheses.

https://doi.org/10.1021/acs.orglett.1c02093
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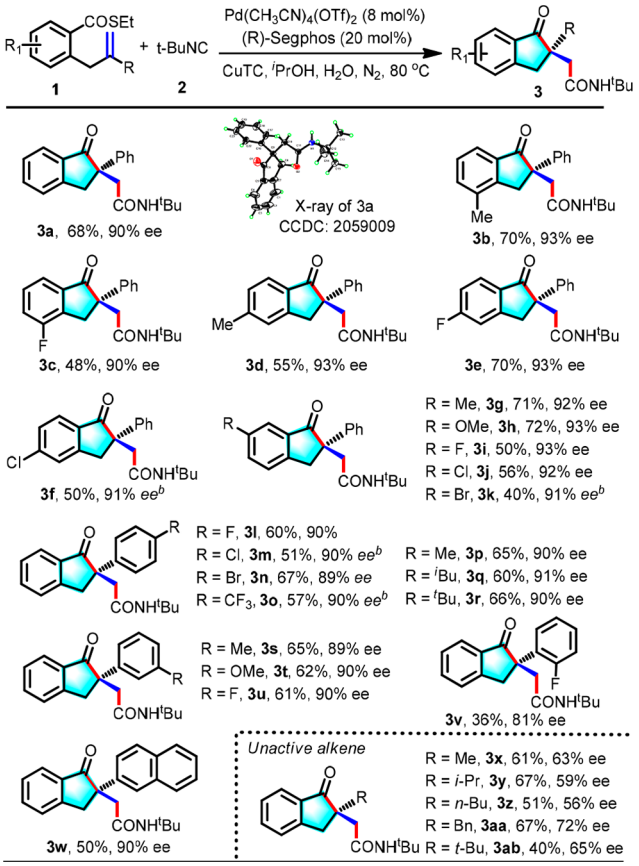
Scheme 2. Construction of Indanone Derivatives[a]



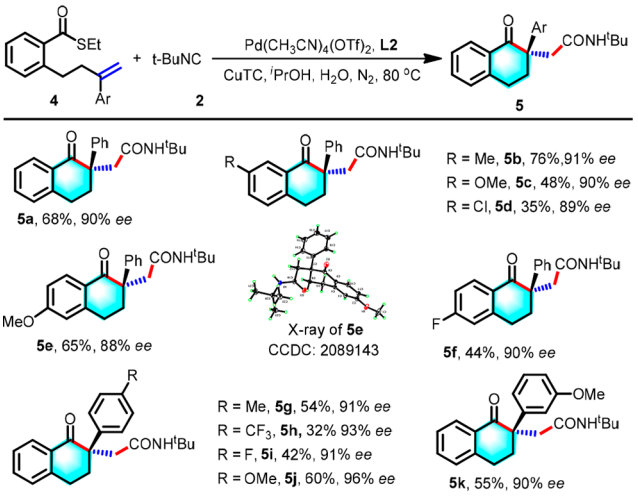
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), Pd-$(CH_3CN)_4(OTf)_2$ (8 mol %), **L4** (20 mol %), CuTC (0.22 mmol), H_2O (20 equiv), ^{i}PrOH (2 mL), N_2, 80 °C. [b]With Pd(CH_3CN)-$(OTf)_2$ (5 mol %), **L4** (12 mol %), and H_2O (5 equiv). Yields of isolated products are given. The ee values were determined by HPLC analysis.

2 was employed, a lower yield and a lower ee value were obtained (**3v**). Substrates bearing naphthyl moieties gave rise to product **3w** in 50% yields with 90% ee. It is worth noting that unactivated alkenes (**1x**−**1ab**) are compatible with our protocol, albeit in lower ee values.

Encouraged by the success with the synthesis of indanone, we applied our protocol to the construction of 1-tetralone derivatives (Scheme 3). However, when **L4** was employed as the ligand, a <5% yield of desired product **5a** was formed. To our delight, after various conditions had been screened (see the Supporting Information), **L2** could afford the desired product in 68% yield with 90% ee. Methyl, methoxyl, and chloro groups in both the thioester fragment and aryl groups on the vinyl moiety were quite compatible, furnishing the corresponding tetralone derivatives in 88−96% ee. (The absolute stereochemistry of **5e** was determined by X-ray analysis.) Substrates bearing fluoride or trifluoromethyl groups, which are prevalent in pharmaceuticals, afforded the fluorine-containing tetralone derivatives (**5f**, **5h**, and **5i**).

To demonstrate the synthetic utility of this protocol, recrystallized optically pure indanone product **3a** could be transformed to a variety of valuable skeletons with the retention of enantiopurity (for details, see the Supporting Information). Witting olefination of the ketone moiety in **3a** could afford indene product **6** in 40% yield with 99% ee.

Scheme 3. Construction of 1-Tetralone Derivatives[a]

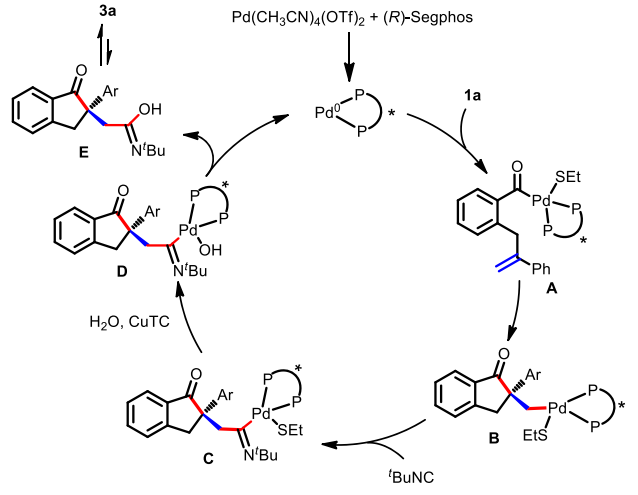


[a]Reaction conditions: **4** (0.1 mmol), **2** (0.1 mmol), Pd-$(CH_3CN)_4(OTf)_2$ (10 mol %), **L2** (20 mol %), CuTC (0.22 mmol), H_2O (50 equiv), ^{i}PrOH (2 mL), N_2, 80 °C, 48 h. Yields of isolated products are given. The ee values were determined by HPLC analysis.

Hydrolysis of amide afforded acid product **7** in 98% yield, which can be further transformed into spiro-ring product **8**, aldehyde **10**, and ketones **11** and **12**.

On the basis of previous reports,[11,16] a plausible mechanism is proposed (Scheme 4). Oxidative addition of Pd(0) with **1a**

Scheme 4. Proposed Mechanism



afforded Pd(II) intermediate **A**. Then intramolecular migratory insertion of the acylpalladium into the alkene forms α-quaternary chiral ketone **B** with the C(sp^3)−Pd species, which subsequently undergo 1,1-migratory insertion to *t*-BuNC to afford intermediate **C**. Hydrolysis of intermediate **C** afforded intermediate **D**. Reductive elimination of **D** afforded the Pd(0) species and intermediate **E**, which further tautomerize to generate product **3a**.

In summary, we have disclosed an efficient protocol for the palladium-catalyzed asymmetric acyl-carbamoylation of alkene, affording five- and six-membered cyclic ketones with α-quaternary chiral stereocenters in moderate to good yields with good to excellent enantioselectivities. The reaction

https://doi.org/10.1021/acs.orglett.1c02093
Org. Lett. XXXX, XXX, XXX−XXX

condition is mild, and a variety of functional groups were tolerated. Product diversifications with retention of enantiopurity make the protocol attractive for the synthesis of some valuable skeletons.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02093.

Experimental procedures, characterization of new compounds, and NMR spectral data and X-ray data of **3a** and **5e** (PDF)

Accession Codes

CCDC 2059009 and 2089143 contain 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.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Shanghai Institute of Materia Medica, the Chinese Academy of Sciences, the National Natural Science Foundation of China (21772211 and 21920102003), the Youth Innovation Promotion Association CAS (2014229 and 2018293), the Institutes for Drug Discovery and Development, Chinese Academy of Sciences (CASIMM0120163006), the Science and Technology Commission of Shanghai Municipality (17JC1405000, 21ZR1475400, and 18431907100), the Program of Shanghai Academic Research Leader (19XD1424600), and the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (2018ZX09711002-006), for financial support.

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