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Pd-Catalyzed Asymmetric Dearomatization of Indoles via Decarbonylative Heck-Type Reaction of Thioesters

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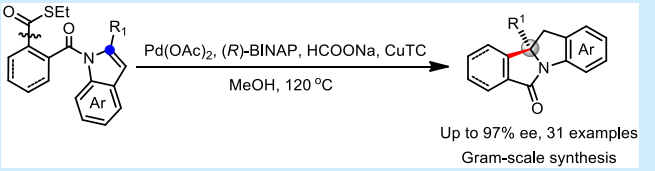
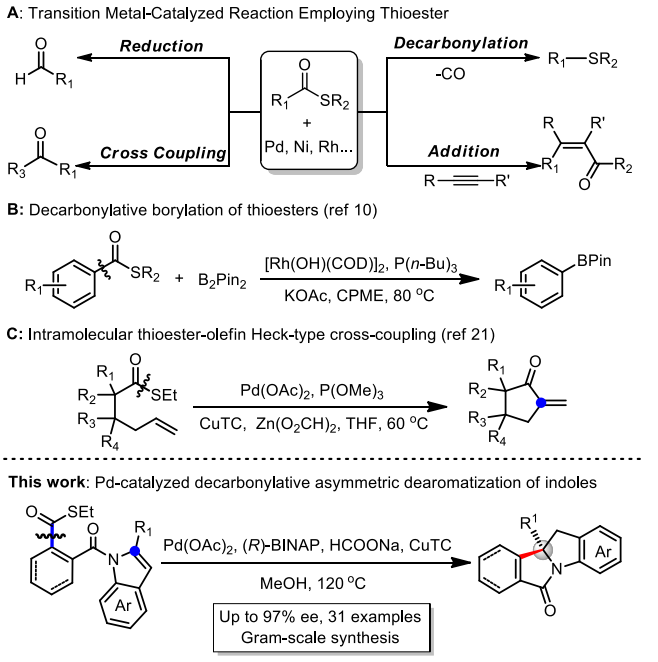
ABSTRACT: We report herein a palladium-catalyzed ligand-promoted asymmetric dearomatization of indoles via the decarbonylation of thioesters and the subsequent reductive Heck reaction. This protocol provides a facile and efficient way to construct an aza-quaternary stereocenter at the C2 position of indolines. A variety of functional groups and substitutions could be well tolerated, affording the substituted indolines with high enantioselectivities.



Thioesters with intriguing chemistry and reactivity are versatile building blocks in organic synthesis[1] and are also often employed as electrophilic acylating reagents in substitution reactions, such as Corey−Nicolaou macrolactonizations[2] and native chemical ligation for peptide connection.[3] Whereas more efforts have been made to develop new reactions employing thioesters, their application in organic synthesis is rare compared with other carboxylic acid derivatives. Transition-metal-catalyzed C−S bond activation paves a new avenue to exploit thioester. Many new transformations have been developed, including reduction to aldehydes,[4] decarbonylation to thioethers,[5] addition to unsaturated bonds,[6] and cross coupling of thioester with organometallic reagents[1a,d7] (Scheme 1A). In 2016, Gu reported a Pd/norbornene/Cu-catalyzed Catellani-type ketone synthesis with thioesters via *ortho*-C−H acylation and *ipso* thiolation of aryl halides.[8] Very recently, Weix reported a novel ketone synthesis by Ni-catalyzed cross-electrophile coupling of thioester with *N*-hydroxyphthalimide (NHP) esters.[9] Thioesters could also be employed as decarbonylative coupling electrophiles. In 2017, Hosoya reported a rhodium-catalyzed decarbonylative borylation of aromatic thioesters with broad functional group tolerance and mild conditions (Scheme 1B).[10]

Indoline with a heteroaromatic bicyclic scaffold is a privileged structural motif,[11] which presents in many natural and biologically active compounds, such as (−)-Mersicarpine,[12] (−)-Isatisine A,[13] and Mollenine A[14] (Figure 1). Catalytic asymmetric dearomatization (CADA), the term coined by You,[15] of indole derivatives has been deemed to be an attractive strategy to readily access sophisticated spiro or fused polycyclic indoline scaffolds with stereochemistry.[16] Exploiting the inherent strong nucleophilicity of indoles at the C3 position to react with various electrophiles is a broadly employed strategy for the asymmetric construction of functionalized indolines.[11a,17] The artful design of the substrates may also trigger cascade asymmetric dearomatization reactions.[18] For example, the groups of Jia[18e] and Zhou[18f]

Scheme 1. Transition-Metal-Catalyzed Reactions Employing Thioesters as Substrates



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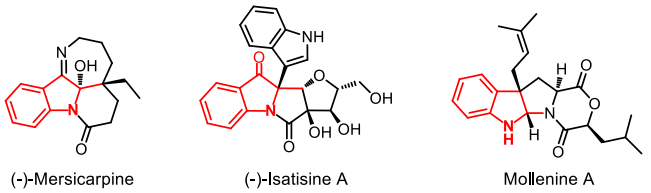


Figure 1. Selected indoline-based natural products containing a C2 quaternary centers.

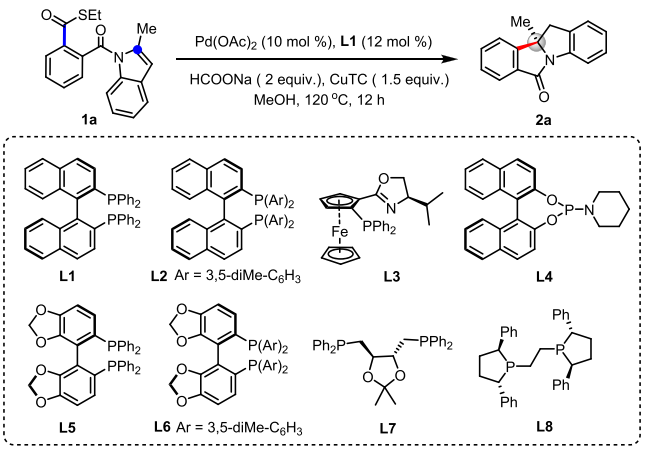
successively disclosed palladium- and nickel-catalyzed intramolecular asymmetric dearomatization via reductive Heck reactions of *N*-(2-halobenzoyl)indoles.

Considering the high importance of the asymmetric dearomatization of indoles and the facility of thioester in the metal-catalyzed transformations, we proposed that the oxidative addition of the Pd(0) to thioesters and subsequently the intramolecular reductive Heck reaction of indoles could construct a stereocenter at the C2 position. To date, the asymmetric construction of valuable cyclic motifs bearing quaternary carbon centers from carbonyl functionalities (for example, thioesters, amide, and ester) is still a big challenge.[19,20] Previously, Du Bois and coworkers reported an intramolecular nondecarbonylative Heck-type reaction of thioester, forming terminal alkenes with prochirality (Scheme 1C).[21] In this Letter, we disclose a palladium-catalyzed ligand-promoted asymmetric dearomatization of indoles via the decarbonylative Heck-type reaction of thioesters, constructing C2 aza-quaternary centers with high enantioselectivities.

We commenced our investigation by choosing *S*-ethyl 2-(2-methylindole-1-carbonyl)benzothioate (**1a**) as the model substrate. After careful optimization of the reaction conditions, including chiral phosphines, the solvent, and the reaction time, we obtained the desired product **2a** in 89% yield with 96% *ee* by treating **1a** with $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP (12 mol %), CuTC (1.5 equiv), and HCOONa (2 equiv) in methanol at 120 °C for 12 h (Table 1, entry 1). A lower catalyst loading led to decreased yields of **1a** (Table S1). Phosphine ligands are often required in the decarbonylation of thioesters.[5d,e10] Among the various chiral ligands, bidentate phosphines gave good to excellent yields (Table 1, entries 2−8), and L1 ((*R*)-BINAP) delivered the best *ee* value (Table 1, entry 1). Although HCOONa gave the best result among the hydride sources examined, a combination of organic amines with HCOOH was also employable (Table S2). A higher yield was obtained by using HCOOH/TMEDA as the hydride source with 92% *ee* (Table 1, entry 9). A hydride source, palladium catalyst, and CuTC are indispensable in the reaction (Table 1, entries 10−12). Lowering the reaction temperature or shortening the reaction time would lead to decreased yields (Tables S5 and S6).

With the optimized reaction conditions in hand, we subsequently explored the substrate scope by examining the substituents at the C2 position of the indoles (Table 2). To our delight, various alkyl groups, including methyl, *n*-butyl, cyclohexyl, and cyclopropyl were compatible, delivering the corresponding products **2a**−**d** in good yields (69−86%) with excellent enantioselectivities (90−96% *ee*). Aryl groups with various substituents at the C2 position of the indoles were also examined, and corresponding products **2e**−**m** could be obtained with good results. Substrates with an ortho- and meta-substituted benzene ring gave the desired products in relatively lower yields, possibly due to the unfavorable steric

Table 1. Screening of Optimal Reaction Conditions[a]



entry	variations from the standard conditions	yield (%)[b]	*ee* (%)[c]
1	none	89	96
2	L2 instead of L1	86	90
3	L3 instead of L1	28	15
4	L4 instead of L1	78	0
5	L5 instead of L1	81	91
6	L6 instead of L1	91	88
7	L7 instead of L1	60	26
8	L8 instead of L1	79	85
9[d]	HCOOH + TMEDA instead of HOONa	92	92
10	without HCOONa		
11	without $Pd(OAc)_2$		
12	without CuTC	<5	

[a]Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), ligand (12 mol %), HCOONa (2.0 equiv), CuTC (1.5 equiv), MeOH (1.0 mL), 120 °C (oil bath), N_2, 12 h. [b]Yield was determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard. [c]Determined by chiral HPLC. CuTC: copper(I) thiophene-2-carboxylate. [d]2.0 equiv. HCOOH and 2.0 equiv. TMEDA were separately added.

hindrance (**2g**, **2h**, **2l**).[18e] Substrates bearing a naphthyl group at the C2 position of the indole furnished the desired product in 67% yield with 96% *ee* (**2n**). To our delight, the protocol could be extended to heterocycle-containing substrates, including furan and thiophene, giving the asymmetric dearomatization products with excellent enantioselectivities (**2o** and **2p**). Moreover, benzyl and ester groups at the C2 position of indoles were also proven to be favorable in the transformation, affording the desired products **2q** and **2r** in good yields with 92 and 91% *ee*, respectively.

Substituents at other positions of indoles were also investigated (Table 3). A substrate bearing electron-donating groups such as methyl, methoxyl, and *t*-butyl would proceed efficiently, giving the desired products in good yields with high *ee* values (**2s**, **2v**, **2w**, **2aa**). The halogen -substituted substrates (**2t** and **2u**) could also be converted into the desired products in satisfactory yields along with excellent enantioselectivities. For those substrates with electron-withdrawing groups, such as trifluoromethyl (**2x**, **2ab**) and nitrile (**2y**), the reaction proceeded with relatively lower yields due to the decomposition of starting material. When the C5 position of the indole moiety was substituted by a phenyl group, the reaction could also give the desired product in moderate yield, despite the extended π-conjugation (**2z**). To our delight, the protocol could be extended to the asymmetric dearomative alkenylation

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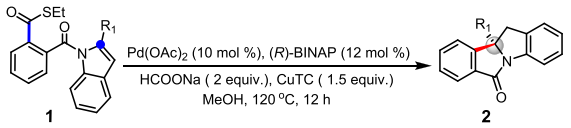
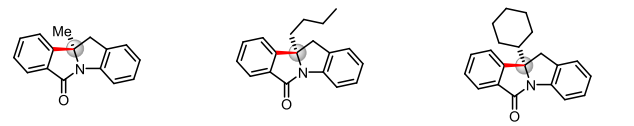
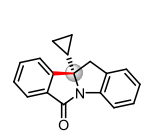
Table 2. Decarbonylative Asymmetric Dearomatization of C2 Position-Derived Indoles[a,b,c]

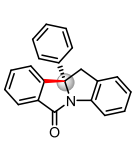


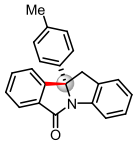

2a, 86% yield, 95% ee

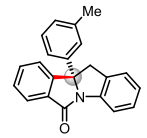
2b, 83% yield, 90% ee

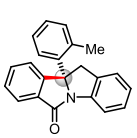
2c, 69% yield, 90% ee

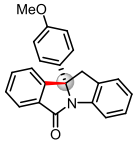

2d, 83% yield, 96% ee

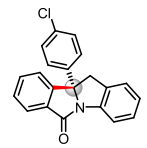

2e, 83% yield, 95% ee

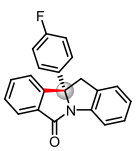

2f, 79% yield, 92% ee

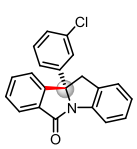

2g, 59% yield, 93% ee

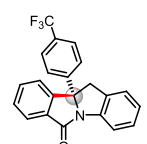

2h, 13% yield, 93% ee

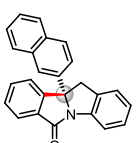

2i, 84% yield, 95% ee

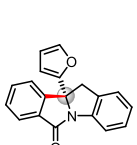

2j, 73% yield, 88% ee

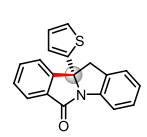

2k, 69% yield, 95% ee

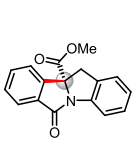

2l, 60% yield, 95% ee

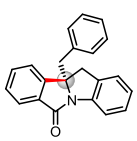

2m, 70% yield, 89% ee


2n, 67% yield, 96% ee


2o, 63% yield, 95% ee

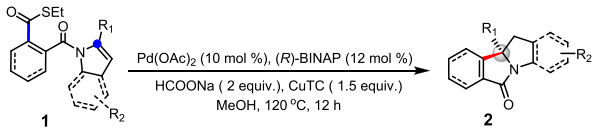

2p, 66% yield, 97% ee

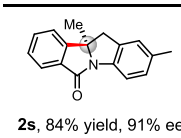

2q, 68% yield, 92% ee

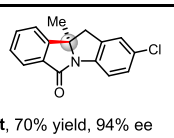

2r, 82% yield, 91% ee

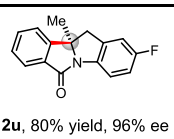
[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP (12 mol %), HCOONa (2.0 equiv), CuTC (1.5 equiv), MeOH (1.0 mL), 120 °C (oil bath), N_2, 12 h. [b]Isolated yield. [c]*ee* values determined by chiral HPLC.

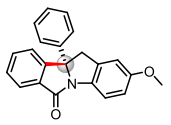
Table 3. Decarbonylative Asymmetric Dearomatization of Other Position-Derived Indoles[a,b,c]

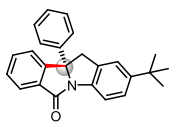


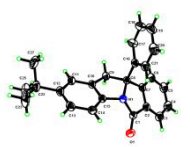

2s, 84% yield, 91% ee

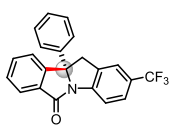

2t, 70% yield, 94% ee

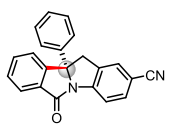

2u, 80% yield, 96% ee

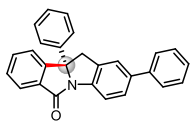

2v, 76% yield, 96% ee

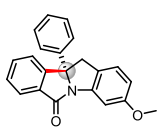

2w, 91% yield, 93% ee

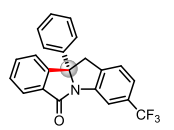


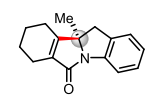

2x, 48% yield, 94% ee

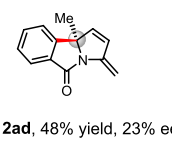

2y, 40% yield, 95% ee

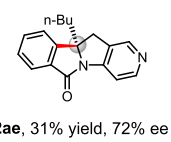

2z, 44% yield, 95% ee

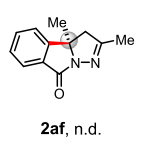

2aa, 72% yield, 89% ee


2ab, 50% yield, 96%ee


2ac, 74% yield, 85% ee


2ad, 48% yield, 23% ee[d]


2ae, 31% yield, 72% ee


2af, n.d.

[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP (12 mol %), HCOONa (2.0 equiv), CuTC (1.5 equiv), MeOH (1.0 mL), 120 °C (oil bath), N_2, 12 h. [b]Isolated yield. [c]*ee* values determined by chiral HPLC. [d]**1ad** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), (S,S,R_a)-Feringa ligand (L11) (12 mol %), K_2CO_3 (2.0 equiv), CuTC (1.5 equiv) in toluene (1 mL) at 70 °C for 12 h.

of indoles by using **1ac** as the substrate. A tetracyclic indoline skeleton **2ac** bearing a C2-alkenylated aza-quaternary stereocenter was obtained in good yield with acceptable enantioselectivity. The absolute configuration of the asymmetric dearomatization product was determined by the X-ray structural analysis of **2w**.

Additionally, a 2,5-dimethyl-1*H*-pyrrole moiety was introduced via an amide bond, and substrate **1ad** was synthesized. Under the standard conditions, no target product was detected; however, when (S,S,R_a)-Feringa ligand (L11) was used instead of (*R*)-BINAP accompanied by K_2CO_3 as the base in toluene, **2ad** could be obtained in 48% yield with 23% *ee*. It was found that the reaction using dppf as the ligand in CH_2Cl_2 could afford **2ad** in 74% yield, albeit in racemic form (Table S9). However, when 3,5-dimethyl-1*H*-pyrazole was introduced via an amide bond under any of the previously mentioned reaction conditions, substrate **1af** rapidly decomposed into 3,5-dimethyl-1*H*-pyrazole and isobenzofuran-1,3-dione probably due to the more active amide bond (Table S10).

Additionally, to demonstrate the endurance of the reaction for the substrates containing other heterocycles, 2-butyl-1*H*-pyrrolo[3,2-*c*]pyridine was synthesized and introduced into substrate **1ae**. It is worth noting that the desired product **2ae** could be obtained in 31% yield with 72% *ee*.

The feasibility of this transformation for the gram-scale synthesis was demonstrated by treating substrate **1a** (1.13 g) with 5 mol % $Pd(OAc)_2$ at 120 °C for 12 h. The desired product **2a** was obtained in 71% yield with 96% *ee* (Scheme 2).

In summary, we have successfully developed a palladium(0)-catalyzed, ligand-promoted asymmetric dearomatization reaction of indole derivatives. Phosphine ligands are crucial in the decarbonylation of thioesters and the subsequent asymmetric reductive Heck process. A variety of functional groups were

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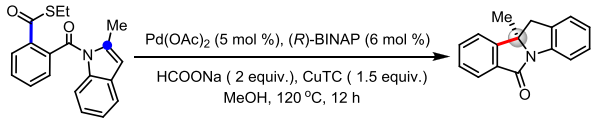
Scheme 2. Gram-Scale Synthesis



1a, 3.50 mmol, 1.13 g

2a, 2.48 mmol, 584 mg
71% yield, 96% ee

tolerated, giving the desired products in moderate to good yields with 23−97% *ee*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03897.

General information, preparation of substrates, NMR spectra, and HPLC spectra (PDF)

Accession Codes

CCDC 2008511 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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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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