

Cu- and Pd-Catalyzed Asymmetric One-Pot Tandem Addition–Cyclization Reaction of 2-(2',3'-Alkadienyl)- β -keto Esters, Organic Halides, and Dibenzyl Azodicarboxylate: An Effective Protocol for the Enantioselective Synthesis of Pyrazolidine Derivatives

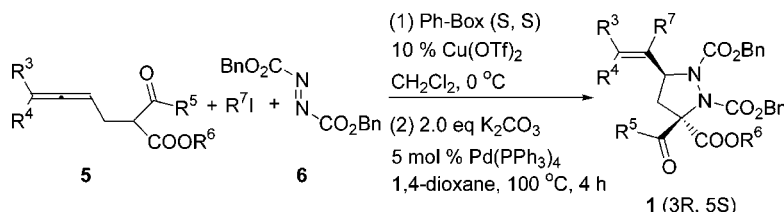
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ABSTRACT



Optically active pyrazolidine derivatives have been constructed by the Cu- and Pd-catalyzed asymmetric one-pot tandem addition–cyclization reaction of 2-(2',3'-dienyl)- β -ketoesters, organic halides, and dibenzyl azodicarboxylate. The absolute configurations of the final products depend on the structure of the ligand.

The development of new chemical processes for producing elaborate and important heterocyclic structures in a rapid, atom-economic,¹ and efficient manner has become an important area of research in organic chemistry. One of the major challenges in these areas is the multicomponent process in which a given target molecule would be assembled from three or more simple and flexible building blocks in a practical one-pot operation.^{2,3}

Pyrazolidines are an intensively studied family of heterocycles, which are important subunits in biologically active naturally occurring compounds.⁴ This pyrazolidine structural

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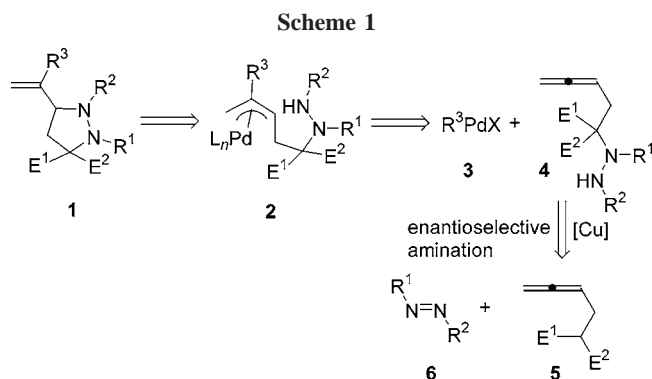
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unit is usually constructed by the [3 + 2] cycloaddition^{5,6} or hetero-Diels–Alder reactions.⁷ Although these methods are available, there are still some obvious limitations: the starting material is complex, and the methods for the synthesis of optically active pyrazolidines are still very limited.

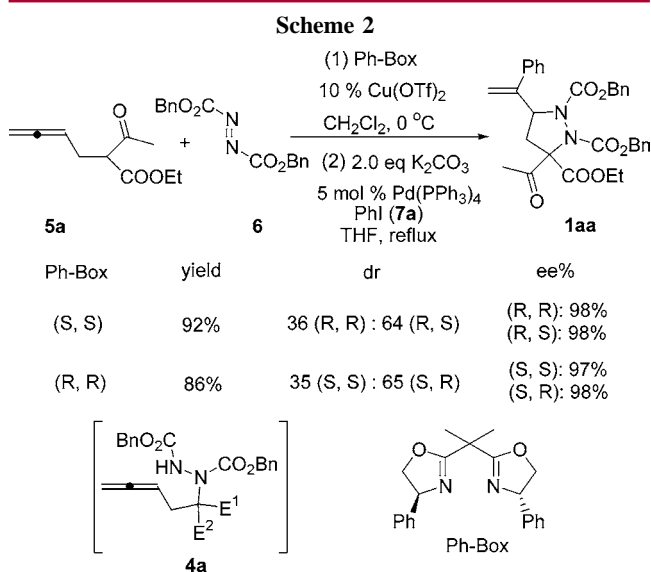
Recently, the direct enantioselective amination of 2-ketoesters catalyzed by chiral copper(II)-bisoxazoline complexes was reported.⁸ On the basis of our past work,^{9,10} we reasoned that pyrazolidines **1** with different substitution patterns may be generally constructed from π -allypalladium intermediate¹¹ **2**, which in turn, could be generated easily via the carbopalladation of intermediate **3** with allene **4**^{12,13} (Scheme 1).



The optically active allene **4** may be produced from enantioselective copper (II)-catalyzed α -amination of α -allenic-substituted β -keto esters **5** with azodicarboxylates **6** (Scheme 1). Herein, we describe the Cu- and Pd-catalyzed one-pot

three-component asymmetric tandem addition–cyclization leading to optically active pyrazolidine derivatives with high selectivity.

Our first approach was based on the reaction of 2-(2',3'-dienyl)- β -ketoesters **5a** and dibenzyl azodicarboxylate (DBAD) **6** with PhI (**7a**). First, the enantioselective amination of **5a** with DBAD **6** in CH_2Cl_2 provided the corresponding optically active allenic amide **4a** ($\text{E}^1 = \text{COCH}_3$; $\text{E}^2 = \text{COOEt}$; $\text{R}^1 = \text{R}^2 = \text{COOBn}$) in quantitative yield. Then, the solvent was removed in vacuo and THF was added to the reaction mixture followed by treatment with PhI, $\text{Pd}(\text{PPh}_3)_4$ (5% mol), and K_2CO_3 (2.0 equiv) under reflux (Scheme 2). The carbopalladation reaction¹⁴ of the allenes afforded a 2-type π -allyl palladium intermediate,¹¹ which can be further trapped by the intramolecular nitrogen giving the corresponding pyrazolidine derivative **1aa** in good overall yields with very high enantioselectivity (Scheme 2). On the



basis of these results, it is quite obvious that the enantioselectivity for the formation of **4a** is very high with the absolute configuration depending on the structure of the ligand.

Although the diastereoselectivity is unsatisfactory, the diastereoisomers differ greatly in terms of molecular polarity ($R_{\text{f(R,R)}-\mathbf{1aa}} = 0.48$, $R_{\text{f(R,S)}-\mathbf{1aa}} = 0.35$; eluent, petroleum ether/ether = 1:1) and therefore can be easily separated and purified by flash chromatography on silica gel. Then, the four pure isomers (*S,S*)-, (*S,R*)-, (*R,R*)-, and (*R,S*)-isomer of **1aa** can be conveniently obtained in high yield with very high ee when both enantiomers of Ph-Box were applied as the ligand.

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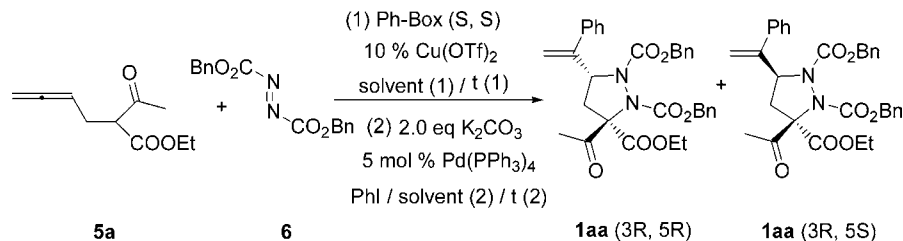
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Table 1. Cu and Pd-Catalyzed Three-Component Asymmetric Tandem Addition–Cyclization Reactions of 2-(2',3'-Dienyl)- β -keto-esters **5a** and Dibenzyl Azodicarboxylate (DBAD) **6** with PhI **7a** in Different Solvents^a



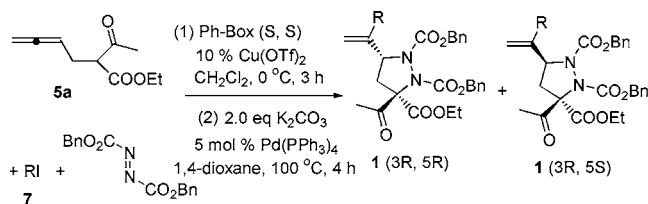
entry	solvent (1)	<i>t</i> (1), °C	time(1), h	solvent (2)	<i>t</i> (2), °C	time (2), h	yield (%)	dr (% ee) (<i>R,R</i>)/(<i>R,S</i>)
1	CH ₂ Cl ₂	0	3	THF	reflux	4	92	36:64 (98:98)
2	THF	0–rt	57	THF	reflux	4	66	48:52 (99:96)
3	CH ₂ Cl ₂	0	3	CH ₂ Cl ₂ /A ^b	reflux	4	92	40:60 (98:98)
4	CH ₂ Cl ₂	0	3	CH ₂ Cl ₂ /B ^b	100	4	85	33:67 (98:98)
5	CH ₂ Cl ₂ /B ^b	rt	3	CH ₂ Cl ₂ /B ^b	100	4	95	32:68 (95:95)
6	CH ₂ Cl ₂	rt	1.5	CH ₂ Cl ₂ /B ^b	100	4	100	37:63 (97:97)
7	CH ₂ Cl ₂ /B ^b	0	10	CH ₂ Cl ₂ /B ^b	100	4	90	36:64 (97:98)
8	CH ₂ Cl ₂ /C ^b	0	20	CH ₂ Cl ₂ /C ^b	100	4	19	76:24 (13:8)
9	CH ₂ Cl ₂ /D ^b	0	20	CH ₂ Cl ₂ /D ^b	100	4	0	0

^a DBAD (1.2 equiv), Ph-Box (1.1 equiv of Cu), PhI (1.2 equiv), and K₂CO₃ (2.0 equiv) were applied. ^b A = THF; B = 1,4-dioxane; C = DMSO; D = DMF. The solvent ratio was 1:2.

To identify a more convenient operation for the reaction, we tested the effect of the solvents of the two steps on the reaction. The results are summarized in Table 1. When both steps were carried out in THF, high enantioselectivity was achieved; however, the yield and diastereoselectivity were unsatisfactory (entry 2, Table 1). When a mixture of CH₂Cl₂/1,4-dioxane (1:2) was used as the solvent in both steps, the results were better (entry 7, Table 1), but the first step was slow (compare entry 7 with entry 4, Table 1). The reaction gave poor results in the mixed solvent of DMSO or DMF and CH₂Cl₂ (entries 8 and 9, Table 1). The temperature in the first step is important to the enantioselectivity (compare entry 4 with entry 6 and entry 5 with entry 7, Table 1). On the basis of these results, CH₂Cl₂ was chosen as the solvent at 0 °C in the first step followed by the direct addition of 1,4-dioxane (double volume of CH₂Cl₂) to the reaction mixture to conduct the second step at 100 °C.

The results of the Cu- and Pd-catalyzed three-component asymmetric tandem addition–cyclization reactions of 2-(2',3'-dienyl)- β -ketoesters **5a** and dibenzyl azodicarboxylate (DBAD) **6** with different organohalides are summarized in Table 2. From these results, it should be noted that (1) the yield and the enantioselectivity of these reactions are high and (2) the configuration of the C=C bond in 1-alkenyl iodide remained unchanged during the reaction (entries 7–9, Table 2). To determine the absolute structure of the pyrazolidine derivative, we studied the reaction of **5a**, **6**, and 1-bromo-4-iodobenzene **7e**, which afforded the solid pyrazolidine derivative **1ae** with a bromine atom in the structure, indicating that the C–I bond was chemoselectively cleaved. The absolute configurations of **1ae** were determined by X-ray diffraction studies,^{15,16} which led to the tentative assignment

Table 2. Cu- and Pd-Catalyzed Three-Component Asymmetric Tandem Addition–Cyclization Reactions of 2-(2',3'-Dienyl)- β -keto-esters **5a** and Dibenzyl Azodicarboxylate (DBAD) **6** with Different Organohalides



entry	RI	7	yield (%)	dr(<i>R,R</i> / <i>R,S</i>)	ee% (<i>R,R</i>)	ee% (<i>R,S</i>)
1	PhI	7a	85 (1aa)	33:67	98	98
2		7b	95 (1ab)	34:66	98	98
3		7c	92 (1ac)	33:67	98	98
4		7d	96 (1ad)	38:62	97	98
5		7e	94 (1ae)	36:64	97	>98
6		7f	97 (1af)	40:60	>98	99
7		7g	98 (1ag)	45:55	97	98
8		7h	86 (1ah)	37:63	99	99
9		7i	75 (1ai)	34:66	97	98
10		7j	71 (1aj)	36:64	91	99

of the absolute configurations of other products. It is obvious that the reaction favors the formation of *trans*-pyrazolidine derivative.

In the reaction, it is valuable to note the following: (1) The reaction that allows a great increase in complexity is atom economic. (2) Although two different metals were used to catalyze the reaction, the operation is convenient with a one-pot operation and the yield is very high. (3) Two diastereomers were easily separated with high ee.

In conclusion, we have demonstrated the Cu- and Pd-catalyzed asymmetric one-pot tandem addition–cyclization

reaction of 2-(2',3'-dienyl)- β -keto esters, organic halides, and dibenzyl azodicarboxylate leading to pyrazolidine derivatives with high enantioselectivity. The advantages of this method are the easy availability and diversity of the starting compounds. Although the diastereoselectivity needs further attention, this study will open a new area for the transition metal-catalyzed chemistry of allenes. Further studies on the scope and synthetic applications of this reaction are being pursued in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) CCDC 232606. Crystal data for compound *cis*-**1ae** (3*R*,5*R*): C₃₂H₃₁N₂O₇Br, MW = 635.50, crystal system, space group orthorhombic, *P*2(1)2(1)2(1), Mo K α , final *R* indices [*I* > 2 σ (*I*)], *R*₁ = 0.0469, w*R*₂ = 0.0813, *a* = 8.9635 (9) Å, *b* = 10.2834 (11) Å, *c* = 32.786 (4) Å, α = 90°, β = 90°, γ = 90°, *V* = 3022.1 (6) Å³, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 18 496/7023 (*R*_{int} = 0.0975), no observation [*I* > 2 σ (*I*)] 3265, parameters 425, absolute structure parameter: −0.001 (7).

(16) CCDC 232607. Crystal data for compound *trans*-**1ae** (3*R*,5*S*): C₃₂H₃₁N₂O₇Br, MW = 635.50, crystal system, space group orthorhombic, *P*2(1)2(1)2(1), Mo K α , final *R* indices [*I* > 2 σ (*I*)], *R*₁ = 0.0629, w*R*₂ = 0.1517, *a* = 9.0453 (7) Å, *b* = 9.5125 (8) Å, *c* = 35.549 (3) Å, α = 90°, β = 90°, γ = 90°, *V* = 3058.7 (4) Å³, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 18 653/7107 (*R*_{int} = 0.0710), no observation [*I* > 2 σ (*I*)] 2796, parameters 357, absolute structure parameter: 0.014 (14).