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Silver/palladium relay catalyzed 1,3-dipole annulation/allylation reactions to access fully substituted allyl imidazolidines

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A silver/palladium relay catalyzed 1,3-dipole annulation/allylation reaction of iminoesters and Baylis-Hillman acetates for the construction of fully substituted allyl imidazolidines is reported. Examination of both iminoesters and Baylis-Hillman acetates affords the fully substituted allyl imidazolidines in high yields and regioselectivities. The three component reaction is triggered by silver-catalyzed 1,3-dipole annulation, followed by the sequential palladium catalyzed allylation. Mechanistic studies reveal that the dual catalytic system plays the key role in the reaction. The developed methodology provides straightforward access to allyl imidazolidines under simple reaction conditions.

Dual catalyst relay catalysis, in the light of the combined use of two different catalysts, provides a powerful strategy for achieving ideal organic synthesis.¹ This is because it can fulfill chemical transformation that can't finished by either of the catalysts solely.² In this system, each catalyst works either cooperatively or independently to realize tandem multi-step synthesis in one pot, which dramatically reduces waste, solvents, time and so on. Despite important progress made in this field, it still remains an unmet challenge to skilfully operate two types of dipolarophilic species resulted from different substrates concomitantly. Thus the development of a novel dual catalyst system is highly desirable.

The Baylis–Hillman acetates have emerged as powerful substrates in organic synthesis,³ which can be employed in allylic substitution reactions by forming π -allylpalladium complexes.⁴ Especially, the catalytic allylic amination, which provides an efficient approach to give natural products and biologically active molecules with an allylamino moiety, has attracted tremendously attention.⁵ The allylic amination reaction can result in two regioselective products (α - and γ -products). Thus chemists are devoted to highly regioselective obtain sole product.⁶ In 2002, Igbal and co-workers reported a

palladium-catalyzed allylic amination of Baylis–Hillman acetates, albeit with moderate regioslectivity ($\alpha/\gamma = 3 : 1 \text{ to } 6 :$ 1).⁷ Next Liu and co-workers improved the regioslectivity by employing [Pd(C₃H₅)Cl]₂/ferrocene-type diphosphine catalytic system.⁸ In 2011, Alper and co-workers reported a palladium/palladium relay catalyzed tandem γ -regioselective amination and intramolecular cyclocarbonylation reaction.⁹ Despite all that, How to extend the substrate-scope of the palladium-catalyzed allylic amination reactions into widely Nnucleophiles is still challenge. On the basis of our interest in domino reaction,¹⁰ we describe herein a silver/palladium relay catalyzed 1,3-dipole annulation/allylation reaction of iminoesters ¹¹ and Baylis-Hillman acetates, providing a series of fully substituted allyl imidazolidines in moderate to good yields and excellent regioslectivities (Scheme 1).

(1) Palladium-catalyzed α -regioselective allylic amination of Baylis-Hillman acetates

$$\begin{array}{c} \text{OAc} & \text{NHAr} \\ \text{R}^{1} \swarrow \text{CO}_{2}\text{R}^{2} & + & \text{ArNH}_{2} \end{array} \xrightarrow{\text{Pd}(0)} \quad \text{R}^{1} \swarrow \text{CO}_{2}\text{R}^{2} \end{array}$$

(2) Palladium-catalyzed γ -regioselective amination reactions of Baylis-Hillman acetates



Scheme 1. Allylic substitution of Baylis–Hillman acetates.

Initially, Baylis–Hillman acetate **1aa** and iminoester **2a** were selected as the model substrates to optimize the reaction conditions. By employing a bimetallic catalyst system consisting of $[Pd(C_3H_5)Cl]_2$ and a Cu complex derived from $Cu(CH_3CN)_4BF_4/PPh_3$, NEt₃ as a base in CH_2Cl_2 at room temperature, the reaction proceeded smoothly to give the corresponding product **3a** in 45% yield and complete regioselectivity (Table 1, entry 1). Screening of catalysts II

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⁺ Footnotes relating to the title and/or authors should appear here.

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suggested that $[Pd(C_3H_5)Cl]_2$ was the best catalyst (Table 1, entries 1-6). Next, different Ag(I) and Cu(I) salts were screened, and showed that AgNTf₂/[Pd(C₃H₅)Cl]₂ dual catalysis was the optimal catalyst system, giving the product **3a** in 47% yield (Table 1, entries 1, 7-10). The examination of different solvents and bases indicated that THF and NEt₃ were best choice (Table 1, entries 11-18). Notably, clear effect of temperature on the reaction was observed (Table 1, entries 19-21). Finally, the evidently improved yield was obtained by increasing the stoichiometry of iminoester **2a** (Table 1, entries 15 22-23). **Table 1**. Optimization of the reaction conditions.^{*a*}

Cat I/PPh

yield (Table 2, entry 17). In addition, iminoesters derived from 4-fluoro, and 4-chlorobenzaldehyde could¹⁰als²⁰/affor²⁰⁶the corresponding products **3r-3s** in 27-60% yields (Table 2, entries 18-19). Next, we employed Baylis–Hillman carbonates **1b** as substrates to proceed the reaction. Various Baylis–Hillman carbonates bearing the electron-withdrawing (Table 2, entries 21-24) and electron-donating groups (Table 2, entry 25) were employed in the reaction, providing the desired products **3** in 37-65% yields. The structures of **3** were characterized by a combination of NMR, HRMS spectra, and single crystal X-ray analysis (**3b**) (*see Supporting Information*).¹² **Table 2**. Substrate scope.^a

 		Cat. II	- 7	CO ₂ Et					
Aco Base, Solvent 8h			MeO ₂ C ₁ , N N Ph 3a CO ₂ Me		Ar	~ ~ ~	PPh ₃ (10 mol %) (10 mol %)	
1aa 2a		$R^{1}O$ $R^{2}L^{1}$ $R^{2}L^{1}$ $N^{-1}CO_{2}Me$			[Pd(C ₃ H ₅)Cl] ₂ (5 mol%)			
entry	cat. I	cat. II	solvent	yield			NEt ₃ THF,	(20 mol%) -10 °C, 8h	MeO ₂ C
-				(%) ^b	1 . 1a R ¹ =Ac; 1b R ¹	2 ¹ = Boc			3
1	$Cu(CH_3CN)_4BF_4$	$[Pd(C_3H_5)Cl]_2$	CH_2CI_2	45	,				
2	$Cu(CH_3CN)_4BF_4$	Pd(OAc) ₂	CH_2CI_2	34	entry	Ar	R^1	R ²	vield(%) ^b
3	$Cu(CH_3CN)_4BF_4$	Pd(PPh ₃) ₄	CH_2CI_2	38	1	Ph	Ac	н	78(3 a)
4	$Cu(CH_3CN)_4BF_4$	$Pd_2(dba)_3.CCl_3$	CH_2CI_2	33	2	л. И-ЕС-Н.	Ac	н	67(3b)
5	$Cu(CH_3CN)_4BF_4$	[Ir(COD)CI] ₂	CH_2CI_2	-	2			 Ц	70(36)
6	$Cu(CH_3CN)_4BF_4$	[Rh(COD)Cl] ₂	CH ₂ Cl ₂	-	3		AC		70(3 C)
7	$Cu(CH_3CN)_4PF_6$	$[Pd(C_3H_5)Cl]_2$	CH ₂ Cl ₂	37	4	4-BrC ₆ Π ₄	AC		50(30)
8	Cu(OTf) ₂	$[Pd(C_3H_5)Cl]_2$	CH_2CI_2	37	5	$4-CNC_6H_4$	Ac	н	65(3e)
9	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	CH_2CI_2	47	6	$4-NO_2C_6H_4$	Ac	Н	44(3f)
10	AgOTf	$[Pd(C_3H_5)Cl]_2$	CH_2CI_2	43	7	$4-OCH_3C_6H_4$	Ac	н	59(3g)
11	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	1,4-dioxane	56	8	$4-CH_3C_6H_4$	Ac	н	62(3h)
12	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	toluene	53	9	$4-^{t}BuC_{6}H_{4}$	Ac	Н	53(3i)
13	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	Et ₂ O	50	10	4-CF₂C ₆ H₄	Ac	н	52(3i)
14	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	59	11	3-CIC _c H ₄	Ac	н	70(3k)
15	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	CH₃CN	51	12	3-EC-H.	Δc	н	64(3I)
16	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	CHCl₃	47	12		Ac	и П	74(3m)
17 [°]	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	49	15	5-ыс ₆ п ₄	AC		74(SIII)
18^a	$AgNTf_2$	$[Pd(C_3H_5)Cl]_2$	THF	56	14	$3-NO_2C_6H_4$	AC	н	37(3n)
19 ^e	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	62	15	$2-CIC_6H_4$	Ac	Н	42(30)
20 [†]	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	67	16	2-BrC ₆ H ₄	Ac	Н	31(3p)
21 ^g	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	54	17	2-thienyl	Ac	Н	61(3q)
22 ^{f,h}	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	78	18	Н	Ac	4-F	60(3r)
23 ^{<i>f</i>,<i>i</i>}	AgNTf ₂	$[Pd(C_3H_5)Cl]_2$	THF	76	19	Н	Ac	4-Cl	27(3 s)
^a Unless otherwise specified, all reactions were carried out					20	Н	Вос	н	49(3a)
using 1aa (0.2 mmol) and 2a (0.6 mmol) at room temperature.					21	$4-FC_6H_4$	Вос	н	58(3b)

using **1aa** (0.2 mmol) and **2a** (0.6 mmol) at room temperature. ^b Isolated yield. ^c Na₂CO₃ (2.0 equiv) as base. ^d NaHCO₃ (2.0 equiv) as base. ^e Reaction temperature: 40 °C. ^f Reaction temperature: -10 °C. ^g Reaction temperature: -20 °C. ^h **2a** (4.0 equiv.) was used.

With optimized reaction conditions in hand, the substrate generality of the reaction was next surveyed. As outlined in Table 2. The Baylis–Hillman acetates **1** derived from the aromatic aldehydes bearing either electron-withdrawing or electron-donating groups in the phenyl rings gave the desired products **3** in moderate to good yields (Table 2, entries 1-15). However, the substitution positions of phenyl rings (*ortho-, meta-,* or *para-*) had certain influence on yields, and *ortho* substituent resulted in lower yields, probably due to the steric hindrance (Table 2, entries 15, 16 vs 3, 4, 11, 13). Baylis–Hillman acetates **1aq** derived from 2-thienyl formaldehyde proceeded smoothly, providing the desired product **3q** in 61%

^{*a*} Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol) and **2** (0.8 mmol) at -10 °C. ^{*b*} Isolated yield.

Boc

Boc

Boc

Boc

н

н

Н

н

4-CIC₆H₄

 $4-BrC_6H_4$

 $4 - NO_2C_6H_4$

 $4-CH_3C_6H_4$

22

23

24

25

Owing to demonstrate the practicality of our method, we performed silver/palladium relay catalyzed 1,3-dipole annulation/allylation reaction at the gram scale, when Baylis-Hillman acetate derived from bromobenzaldehyde **1ab** and iminoester **2a** were used in the presence of the low loading of $[Pd(C_3H_5)Cl]_2$, the reaction proceeded smoothly to afford the desired adduct **3b** in 55 % yield at 21h.

44(3c)

65(**3d**)

51(3f)

37(3h)

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$\begin{array}{c} Br \\ AcO + CO_2Et \\ AcO + CO_2Et \\ 1ab \\ 4 \text{ mmol} \end{array} + Ph CO_2Me \\ \begin{array}{c} PPh_3 (10 \text{ mol}\%) \\ AgNTf_2 (10 \text{ mol}\%) \\ Ph \\ AgNTf_2 (10 \text{ mol}\%) \\ Ph \\ CO_2Et \\ Ph \\ NEt_3 (20 \text{ mol}\%) \\ THF, -10 \ ^{\circ}C \\ 3b 1.37g \\ yield: 55\% \end{array}$



In order to verify the reaction mechanism, we carried out some control experiments. First, only silver catalyst and PPh₃ were used, the reaction didn't occur. Next, we proceeded the reaction step by step. The first annulation reaction could proceed smoothly in the presence of silver and PPh₃. While the subsequent reaction could occur only $[Pd(C_3H_5)Cl]_2$ and PPh₃ were applyied, albeit with longer reaction time and lower yield (Scheme 3).



Scheme 3. Control experiment.

Based on our experiment result and previous literature, ^{8,9,13} a possible catalytic model was proposed. As depicted in Scheme 4. The in situ formed azomethine ylide coordinated to the active Ag(I) complex, leading to the intermediate **A**. Conjugate addition of the enolate to another iminoester gave the enolate intermediate **B**. The following intramolecular annulation produced the intermediate **C**. And the formation of Pd(II)/PPh₃ complex activated the Baylis–Hillman acetate **1aa** affording the intermediate **D**, which removed monomolecular acetic acid to give the intermediate **E**. Next, intermediate **F** was obtained by coordinating [Pd] with imidazolidinide anion. Finally, the desired product **3a** was obtained by γ regioselective allylic substitution reaction (Scheme 4). $\rho_{T} \sim co_{eMe} + E_{V}$



Scheme 4. A proposed mechanism.

Conclusions

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We developed a silver/palladium relay catalyzed 1,3-dipole annulation/allylation reaction of iminoesters and Baylis-Hillman acetates, providing the corresponding *tri*-substituted alkenes **3** in moderate to good yields and excellent regioselectivities. The gram scale experiment demonstrated the practicality of our method. It should be noted that the reaction owned lower reactive activity step by step, which certificated the effectiveness of the Ag/Pd relay catalysis system.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (c) J. Zhou, Multicatalyst System in Asymmetric Catalysis (Wiley)., 2014; (d) T. L. Lohr, and T. J. Marks, *Nat. Chem.*, 2015, **7**, 477; (e) T.-Y. Shang, L.-H. Lu, Z. Cao, Y. Liu, W.-M. He and B. Yu, *Chem. Commun.*, 2019, **55**, 5408.
- 2 Selected examples, see: (a) A. R. O. Venning, M. R. Kwiatkowski, J. E. Roque Peña, B. C. Lainhart, A. A. Guruparan, E. J. Alexanian, J. Am. Chem. Soc., 2017, 139, 11595; (b) M. Bakos, Á. Gyömöre, A. Domján and T. Soós, Angew. Chem. Int. Ed., 2017, 56, 5217; (c) A. Kondoh and M. Terada, Org. Lett., 2018, 20, 5309; (d) J. Meng, L.-F. Fan, Z.-Y. Han and L.-Z. Gong, Chem, 2018, 4, 1047; (e) P. Chen, Z.-C. Chen, Y. Li, Q. Ouyang, W. Du and Y.-C. Chen, Angew. Chem. Int. Ed., 2019, 58, 4036; (f) Z.-C. Chen, Z.-H. Yang, L. Guo, W. Du, and Y.-C. Chen, Angew. Chem. Int. Ed., 2019, 58, 15021.
- For selected reviews, see: (a) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447; (b) R. Rios, *Catal. Sci. Technol.*, 2012, **2**, 267; (c) T.-Y. Liu, M. Xie and Y.-C. Chen, *Chem. Soc. Rev.*, 2012, **41**, 4101; (d) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659; (e) P. Xie and Y. Huang, *Org. Biomol. Chem.*, 2015, **13**, 8578.
- 4 (a) B. M. Trost, M. R. Machacek and A. Aponick, Acc. Chem. Res., 2006, **39**, 747; (b) B. M. Trost and F. D. Toste, J. Am. Chem. Soc., 1998, **120**, 815; (c) B. M. Trost, H. C. Tsui and F. D. Toste, J. Am. Chem. Soc., 2000, **122**, 3534; (d) L.-Z. Yu, Z.-Z. Zhu, X.-B. Hu, X.-Y. Tang and M. Shi, Chem. Commun., 2016, **52**, 6581; (e) Y. Wang, S. Jia, E.-Q. Li, and Z. Duan, J. Org. Chem., 2019, **84**, 15323.
- (a) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (b) G. Helmchen, A. Dahnz, P. Dubon, M. Schelwies and R. Weihofen, *Chem. Commun.*, 2007, 675; (c) M. Diéguez and O. Pàmies, *Acc. Chem. Res.*, 2010, **43**, 312; (d) J. F. Hartwig and L. M. Stanley, *Acc. Chem. Res.*, 2010, **43**, 1461.
- 6 Selected examples, see: (a) X. Wang, F. Meng, Y. Wang, Z. Han, Y.-J. Chen, L. Liu, Z. Wang, and K. Ding, Angew. Chem.

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Int. Ed., 2012, **51**, 9276; (b) D. Basavaiah and D. M. Reddy, Org. Biomol. Chem., 2012, **10**, 8774; (c) X. Wang, P. Guo, Z. Han, X. Wang, Z. Wang, and K. Ding, J. Am. Chem. Soc., 2014, **136**, 405; (d) P. Zhou, Y. Liang, H. Zhang, H. Jiang, K. Feng, P. Xu, J. Wang, X. Wang, K. Ding, C. Luo, M. Liu and Y. Wang, Eur. J. Med. Chem., 2018, **144**, 817; (e) Y.-C. Gong, Y. Wang, E.-Q. Li, H. Cui and Z. Duan, Adv. Synth. Catal., 2019, **361**, 1389.

- 7 S. Rajesh, B. Banerji and J. Iqbal, J. Org. Chem., 2002, 67, 7852.
- 8 Y. Wang, L. Liu, D. Wang and Y.-J. Chen, Org. Biomol. Chem., 2012, 10, 6908.
- 9 H. Cao, T. O. Vieira and H. Alper, Org. Lett., 2011, 13, 11.
- 10 (a) Q.-Z. Xi, Z.-J. Gan, E.-Q. Li and Z. Duan, *Eur. J. Org. Chem.*, 2018, 2018, 4917; (b) Z. Gan, Y. Gong, Y. Chu, E.-Q. Li, Y. Huang and Z. Duan, *Chem. Commun.*, 2019, 55, 10120; (c) M. Zhi, Z. Gan, R. Ma, H. Cui, E.-Q. Li, Z. Duan and F. Mathey, *Org. Lett.*, 2019, 21, 3210; (d) Z. Gan, M. Zhi, R. Han, E.-Q. Li, Z. Duan and F. Mathey, *Org. Lett.*, 2019, 21, 3210; (d) Z. Gan, M. Zhi, R. Han, E.-Q. Li, Z. Duan and F. Mathey, *Org. Lett.*, 2019, 21, 2782; (f) R. Ma, G. Song, Q. Xi, L. Yang, E.-Q. Li and Z. Duan, *Chin. J. Org. Chem.*, 2019, 39, 2196.
- Selected reviews about iminoesters, see: (a) E. E. Maroto, M. Izquierdo, S. Reboredo, J. Marco-Martínez, S. Filippone and N. Martín, Acc. Chem. Res., 2014, 47, 2660; (b) J. Adrio and J. C. Carretero, Chem. Commun., 2014, 50, 12434; (c) T. Hashimoto and K. Maruoka, Chem. Rev., 2015, 115, 5366; (d) B. Bdiri, B.-J. Zhao and Z.-M. Zhou, Tetrahedron: Asymmetry, 2017, 28, 876; (e) X. Fang and C.-J. Wang, Org. Biomol. Chem., 2018, 16, 2591.
- 12 CCDC 1960936 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- 13 J. Park, R. Heo, J.-Y. Kim, B. W. Yoo, and C. M. Yoon, *Bull. Korean Chem. Soc.*, 2009, **30**, 1195.

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