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Brønsted Acid Accelerated Pd-Catalyzed Direct Asymmetric Allylic Alkylation of Azlactones with Simple Allylic Alcohols: A Practical Access to Quaternary Allylic Amino Acid Derivatives

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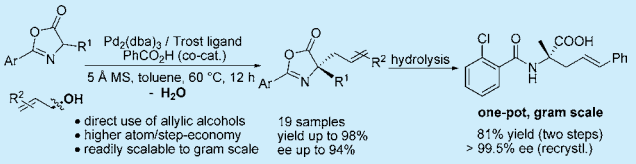
Supporting Information

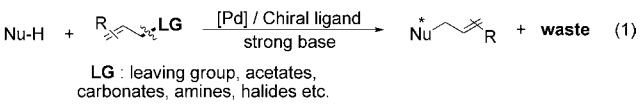
ABSTRACT: A Brønsted acid accelerated Pd-catalyzed asymmetric allylic alkylation of azlactones with simple allylic alcohols under mild reaction conditions has been realized, which provides a direct and readily scalable approach for the synthesis of all-carbon quaternary allylic amino acid derivatives in excellent yields and good enantioselectivities.



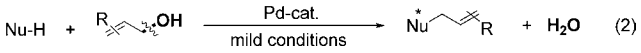
Development of straightforward and atom/step-economic approaches for enantioselective C−C bond formation from readily available starting materials is a fundamental goals in the area of chemical synthesis.[1] Among these strategies, Pd-catalyzed asymmetric allylic alkylation (AAA) represents a powerful synthetic tool and has been widely utilized in organic synthesis.[2] Conventionally, AAA reactions involve activated allylic alcohol derivatives, for instance, carbonates, amines, acetates, and halides, as a π-allyl fragment source, which require an equivalent strong base and inevitably result in stoichiometric waste (Scheme 1, eq 1).[3] From the viewpoint of environmental

Scheme 1. Profile of AAA Reaction

Conventional AAA Reaction:



Atom/step-economic AAA Reaction: *Challenging*



issues and atom/step economy, undoubtedly, the direct use of allylic alcohol itself instead of its derivatives is much more practical due to only water being formed as a byproduct (Scheme 1, eq 2). However, presumably because of the poor reactivity of allylic alcohol, examples of such reactions are very sparse.[4] A breakthrough was made by the Trost group in 2006.[4a] They succeeded in the direct AAA reaction of indoles with allylic alcohols by using stoichiometric amounts of borane as the critical promoter. Quite recently, significant achievements based on chiral phosphoric acid assisted Pd-catalysis and a multicatalyst strategy were reported by List,[4b] Gong,[4c] and Zhang[4d] independently. They successfully extended such transformations to other available nucleophiles such as aldehydes, pyrazol-5-ones, and ketones. Despite these important advances, the direct use of simple allylic alcohols for an efficient AAA reaction under mild reaction conditions remains a great challenge. Further exploration of the useful methodology for other biologically important compounds is of great interest and significance.

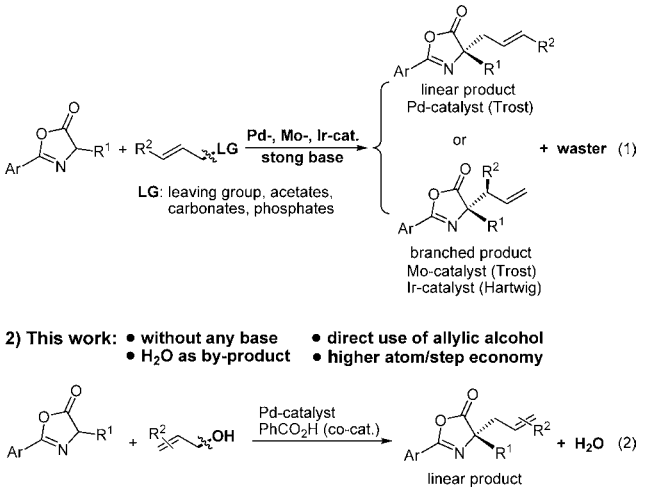
A quaternary amino acid is not only a prominent structural motif found in numerous natural products with vital biological activities but also a very important class of valuable synthetic blocks in organic chemistry.[5] Among the numerous methods for its synthesis, the transition-metal-catalyzed AAA reaction of azlactones provides a facile access to quaternary allylic amino acids, and the introduced double bond makes its further functionalization particularly versatile. Remarkable progress has come from the Trost group[6] and Hartwig group.[7] They developed Pd-, Mo-, and Ir-catalysts for the AAA reaction of azlactones, independently (Scheme 2, eq 1). Nevertheless, these methods need stoichiometric amounts of bases or special additives and simultaneously generate stoichiometric waste. Therefore, the direct use of allylic alcohol to undergo the useful transformation is highly desired. Herein, we report a Brønsted acid accelerated Pd-catalyzed direct and readily scalable method for the AAA reaction of azlactones with allylic alcohols (Scheme 2, eq 2), which provides a more concise and practical entry to linear quaternary allylic amino acid derivatives.

Initially, we treated azlactone **1a** with cinnamic alcohol **2a** in the presence of 3.0 mol % of $Pd_2(dba)_3$, 7.0 mol % of Trost ligand **P-1**, and 5 Å molecular sieves (5 Å MS) in toluene at 60 °C for 12 h. The reaction furnished the desired product **3aa** in

Received: August 28, 2014
Published: September 29, 2014

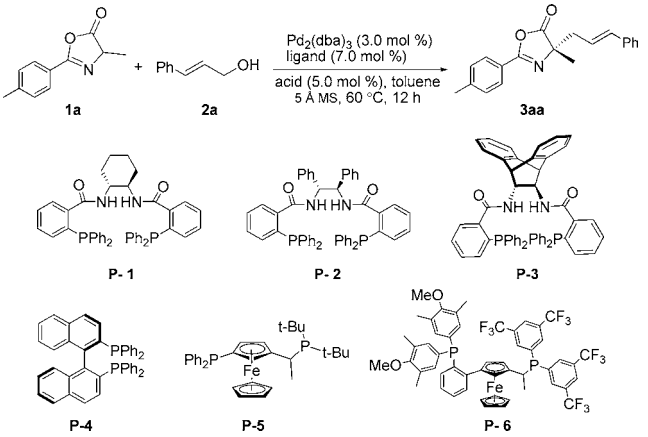
dx.doi.org/10.1021/ol502535z | *Org. Lett.* 2014, 16, 5350−5353

Scheme 2. Asymmetric Allylation of Azlactones



30% yield and 82% ee (Table 1, entry 1). Gratifyingly, adding 5.0 mol % of $PhCO_2H$ accelerated the reaction, affording **3aa** in 95% yield and 84% ee (entry 2), in which $PhCO_2H$ might activate cinnamic alcohol **2a** by hydrogen bonding to expel the hydroxyl group, followed by insertion of a Pd(0) catalyst for the generation of the key π-allyl-Pd intermediate.[4b,c,8] Use of CF_3CO_2H and $(PhO)_2PO_2H$ led to similar enantioselectivities

Table 1. Optimization of Reaction Conditions[a]



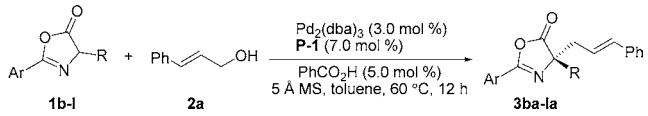
entry	ligand	acid	yield (%)	ee (%)
1	**P-1**	–	30	82
2	**P-1**	$PhCO_2H$	95	84
3	**P-1**	CF_3CO_2H	97	81
4	**P-1**	$(PhO)_2PO_2H$	68	85
5[b]	**P-1**	$PhCO_2H$	45	90
6	**P-2**	$PhCO_2H$	97	59
7	**P-3**	$PhCO_2H$	77	11
8	**P-4**	$PhCO_2H$	36	16
9	**P-5**	$PhCO_2H$	66	15
10	**P-6**	$PhCO_2H$	N.R.[c]	–
11[d]	**P-1**	$PhCO_2H$	90	77
12[e]	**P-1**	$PhCO_2H$	86	83

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $Pd_2(dba)_3$ (3.0 mol %), ligand (7.0 mol %), acid (5.0 mol %), 5 Å MS (50 mg), toluene (2.0 mL), 60 °C, 12 h; all yields are isolated; ee were determined by HPLC analysis. [b]At 40 °C. [c]N.R. means no reaction. [d]$(Allyl)_2Pd_2Cl_2$ was used instead of $Pd_2(dba)_3$. [e]Without 5 Å MS.

(entries 3 and 4). Lowering the reaction temperature from 60 to 40 °C increased the enantioselectivity to 90% but decreased the yield to 45% (entry 5). Changing the ligand to **P-2**–**P-6** resulted in an adverse effect in the reaction (entries 6–10). The replacement of $Pd_2(dba)_3$ with $(allyl)_2Pd_2Cl_2$ resulted in a 90% yield and 76% ee (entry 11). **3aa** was isolated in 86% yield and 83% ee in the absence of 5 Å MS (entry 12). Control experiments including solvent and desiccant examinations did not improve the reaction (for details, see Supporting Information).

Under the optimized reaction conditions, the substrate scope with respect to both azlactones and allylic alcohols was investigated to evaluate the generality of the reaction. First, we were pleased to find that a range of azlactones is quite applicable to the straightforward allylic alkylation reaction. As summarized in Table 2, using **2a** as the allylic reagent,

Table 2. Substrate Scope of Azlactones[a]



entry	Ar	R	3	yield (%)	ee (%)
1	Ph	Me	**3ba**	82	77
2	Ph	Bn	**3ca**	85	81
3[b]	4-MeC_6H_4	$(C_3H_5)CH_2$	**3da**	87	81
4[b]	4-MeC_6H_4	C_3H_5	**3ea**	93	88
5[b]	4-MeC_6H_4	C_6H_{11}	**3fa**	85	88
6[b]	4-MeC_6H_4	4-$CF_3C_6H_4CH_2$	**3ga**	91	78
7	2-ClC_6H_4	Me	**3ha**	98	90
8	4-ClC_6H_4	Me	**3ia**	98	84
9	4-ClC_6H_4	*i*-Pr	**3ja**	95	93
10	4-ClC_6H_4	$(CH_3)_2CHCH_2$	**3ka**	92	86
11	4-ClC_6H_4	Bn	**3la**	80	82

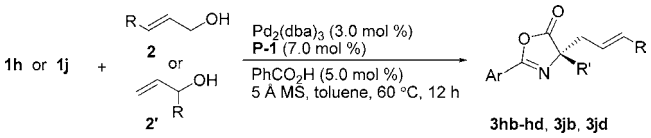
[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), $Pd_2(dba)_3$ (3.0 mol %), **P-1** (7.0 mol %), acid (5.0 mol %), 5 Å MS (50 mg), toluene (2.0 mL), 60 °C, 12 h; all yields are isolated; ee were determined by HPLC analysis. [b]$Pd_2(dba)_3$ (10.0 mol %), **P-1** (22.0 mol %).

azlactones **1b**–**l** gave the desired products **3ba**–**la** in high yields with good enantioselectivities. Phenyl-substituted azlactones **1b** and **1c** afforded the products **3ba** and **3ca** in 82–85% yield and 77–81% ee, respectively (entries 1 and 2). The substrates containing a methyl group at the para position that seem less reactive underwent the reaction with good outcomes, although an increased catalyst loading to 10 mol % was required (entries 3–6). Azlactones bearing a chlorophenyl group, **1h**–**l**, under the standard reaction conditions afforded **3ha**–**la** in 80–98% yields and 82–93% ee (entries 7–11).

Next, a range of functionalized allylic alcohols was employed under the standard reaction conditions. Accordingly, the treatment of **1h** or **1j** with substituted allylic alcohols **2**/**2′** facilely furnishes the allylated products **3hb**–**hd**, **3jb**, and **3jd** in excellent yields and good enantioselectivities (Table 3). It is noteworthy that both electron-withdrawing and -donating groups at allylic alcohols are well tolerated (entries 1–3). Importantly, in contrast to linear allylic alcohols **2a** and **2b**, branched allylic alcohols **2e′** and **2f′** are also suitable for the practical allylation process, and the reactions afforded exclusively linear allylated products **3ha** and **3hb** in similar yields and enantioselectivities (entries 4 and 5), which reveal that the reaction might require a cationic π-allylpalladium(II)

dx.doi.org/10.1021/ol502535z | Org. Lett. 2014, 16, 5350–5353

Table 3. Substrate Scope of Allylic Alcohols[a]



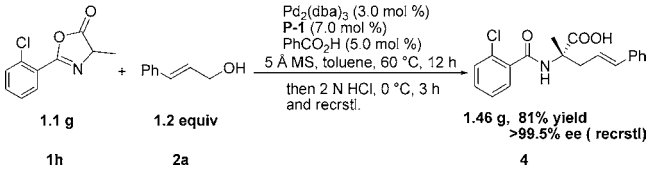
entry	substates	R	3	yield (%)	ee (%)
1	**1h/2b**	4-$MeOC_6H_4$	**3hb**	95	88
2	**1h/2c**	4-ClC_6H_4	**3hc**	98	86
3	**1h/2d**	4-$CF_3C_6H_4$	**3hd**	89	76
4	**1h/2e′**	C_6H_5	**3ha**	93	90
5	**1h/2f′**	4-$MeOC_6H_4$	**3hb**	93	87
6	**1j/2b**	4-$MeOC_6H_4$	**3jb**	93	90
7	**1j/2d**	4-$CF_3C_6H_4$	**3jd**	88	94

[a]Reaction conditions: **1h** or **1j** (0.1 mmol), **2** or **2′** (0.12 mmol), $Pd_2(dba)_3$ (3.0 mol %), **P-1** (7.0 mol %), acid (5.0 mol %), 5 Å MS (50 mg), toluene (2.0 mL), 60 °C, 12 h; all yields are isolated; ee were determined by HPLC analysis.

intermediate to facilitate acquiring a linear product regioselectively.[6c] The reactions of **1j** and **2b/2d** gave better results, affording **3jb** and **3jd** in 88−93% yields and 90−94% ee, respectively (entries 6 and 7).

Remarkably, the direct allylic alkylation reaction can be easily scaled up to gram scale. Consequently, the "one-pot" gram-scale reaction of **1h** (1.1 g) with 1.2 equiv of **2a** under the standard reaction conditions followed by *in situ* hydrolysis smoothly provided the all-carbon quaternary allylic amino acid derivative **4** in 81% yield and >99.5% ee after a single recrystallization (Scheme 3).

Scheme 3. "One-Pot" Gram-Scale Reaction



In summary, we have demonstrated a direct and concise allylic alkylation of azlactones with simple allylic alcohols catalyzed by the combination of a palladium complex with a commercially available Trost ligand and $PhCO_2H$ under mild conditions, which provides a straightforward and practical access to allylic amino acid derivatives. Importantly, the protocol can be easily extended to gram scale. An all-carbon quaternary allylic amino acid derivative was smoothly obtained in 81% yield and >99.5% ee after a single recrystallization which would exhibit great potential and be of significance in the synthesis of biologically active molecules. Further applications of the useful method to the total synthesis of some interesting natural products are under investigation in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details and characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Hundred Talent Program of Chinese Academy of Sciences (CAS) and the National Natural Science Foundation of China (21202175) is gratefully acknowledged.

■ REFERENCES

(1) For selected reviews, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 27. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (d) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (e) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(2) (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317. (d) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258; *Angew. Chem.* **2008**, *120*, 264. (e) Norsikian, S.; Chang, C.-W. *Curr. Org. Synth.* **2009**, *6*, 264. (f) Montserrat, D.; Oscar, P. *Acc. Chem. Res.* **2010**, *43*, 312. (g) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (h) Zhang, W.; Liu, D. In *Chiral Ferrocenes in Asymmetric Catalysis: Synthesis and Applications*; Dai, L.-X., Hou, X.-L., Eds.; Wiley-VCH: Weinheim, 2010; Chapter 14. (i) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (j) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185. (k) Trost, B. M. *Top. Organomet. Chem.* **2013**, *44*, 1.

(3) For recent selected advances, see: (a) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (b) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (c) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343. (d) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493. (e) Trost, B. M.; Miller, J. R.; Hoffman, C. M., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 8165. (f) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354. (g) Chen, J.-P.; Peng, Q.; Lei, B.-L.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2011**, *133*, 14180. (h) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164. (i) Trost, B. M.; Thaisrivongs, D. A.; Hansmann, M. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11522. (j) Bartlett, M. J.; Turner, C. A.; Harvey, J. E. *Org. Lett.* **2013**, *15*, 2430. (k) Yu, Y.; Yang, X.-F.; Xu, C.-F.; Ding, C.-H.; Hou, X.-L. *Org. Lett.* **2013**, *15*, 3880. (l) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626. (m) Quan, M.; Butt, N.; Shen, J.; Shen, K.; Liu, D.; Zhang, W. *Org. Biomol. Chem.* **2013**, *11*, 7412. (n) Huo, X.; Quan, M.; Yang, G.; Zhao, X.; Liu, D.; Liu, Y.; Zhang, W. *Org. Lett.* **2014**, *16*, 1570. (o) Butt, N.; Liu, D.; Zhang, W. *Synlett* **2014**, 615. (p) Garcia, M. A.; Frey, W.; Peters, R. *Organometallics* **2014**, *33*, 1068.

(4) (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (c) Tao, Z.-L.; Zhang, W.-Q.; Chen, D.-F.; Adele, A.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 9255. (d) Huo, X.; Yang, G.; Liu, D.; Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 6776. For another recent notable example for the direct allylation of α-branched aromatic aldehydes with allylic alcohols catalyzed by dual-catalytic strategy, see: (e) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. For a review for Pd-catalyzed reactions of allylic alcohols, see: (f) Muzart, J. *Tetrahedron* **2005**, *61*, 4179.

(5) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I.;

Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (f) Sugiura, M.; Hirano, K.; Kobayashi, S. *Org. Synth.* **2006**, *83*, 170. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (h) McConathy, J.; Goodman, M. M. *Cancer Metastasis Rev.* **2008**, *27*, 555. (i) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (j) Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013**, *15*, 3134.

(6) (a) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (b) Trost, B. M.; Heinemann, C.; Ariza, X.; Weigand, S. *J. Am. Chem. Soc.* **1999**, *121*, 8667. (c) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (d) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256.

(7) (a) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2068. (b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377.

(8) Examples for Brønsted acid accelerated Pd-catalyzed symmetric allylic alkylation: (a) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (b) Patil, N. T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 3101. (c) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241. (d) Jiang, G.; List, B. *Adv. Synth. Catal.* **2011**, *353*, 1667. More recently, Tunge et al. reported a CO_2-assisted Pd-catalyst for allylation reaction using allylic alcohol: Lang, S. B.; Locascio, T. M.; Tunge, J. A. *Org. Lett.* **2014**, *16*, 4308.

dx.doi.org/10.1021/ol502535z | *Org. Lett.* 2014, 16, 5350−5353