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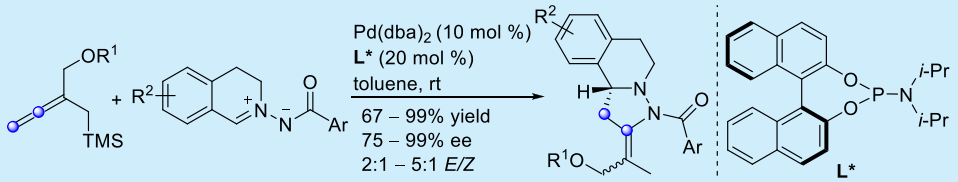
Palladium-Catalyzed Asymmetric Tandem [3+2] Cycloaddition/Allylation Reaction of Methylene-Trimethylenemethane: Access to Chiral Tricyclic Dinitrogen-Fused Heterocycles

Biming Mao, Yi Xu, Yuehua Chen, Jipan Dong, Junya Zhang, Kejia Gu, Bing Zheng, and Hongchao Guo*

Department of Applied Chemistry, China Agricultural University, Beijing 100193, P. R. China

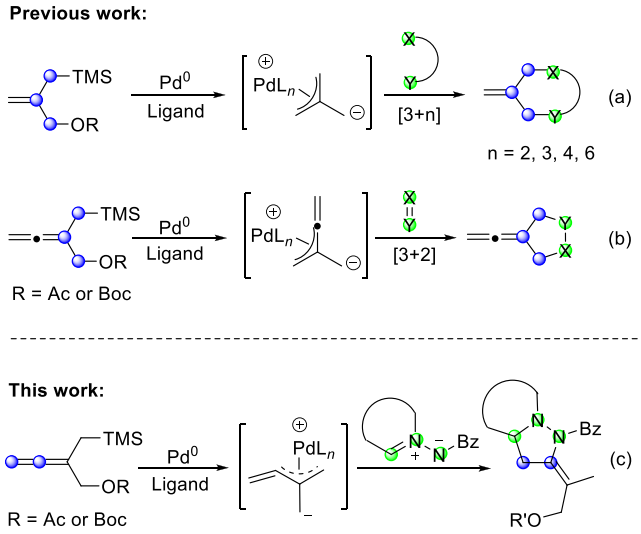
Supporting Information



ABSTRACT: A palladium-catalyzed asymmetric tandem [3+2] cycloaddition/allylation of methylene-trimethylenemethane is presented, providing the functionalized chiral hexahydropyrazolo[5,1-*a*]isoquinoline derivatives in high yields with good to excellent enantioselectivities and moderate to good *E*:*Z* ratios. In the one-pot sequential tandem reactions/hydroxylation, (*E*)-allylic alcohol products were obtained in good yields with excellent enantioselectivities.

The cycloaddition reactions of palladium-trimethylenemethane (Pd-TMM) are very useful tools for the synthesis of cyclic compounds[1] and the total synthesis of natural products.[2] In Pd-TMM chemistry, allyl trimethylsilanes had extensively been employed as TMM donors for the synthesis of various substituted carbocycles[3] and heterocycles[4] since Trost's important contribution in 1979[5] (Scheme 1a). To further extend Pd-TMM chemistry, in 2013, Trost synthesized allenylmethyl-substituted trimethylsilane, which was used as a donor of Pd-methylene-TMM, and reported palladium-catalyzed [3+2] cycloaddition of a methylene-TMM donor with α,β-unsaturated *N*-acyl pyrroles, providing substituted vinylidenecyclopentanes in excellent yields and enantioselectivities (Scheme 1b).[6] Recently, they used this methodology to produce a wide variety of substituted chiral allenes.[7] In Pd-TMM and Pd-methylene-TMM chemistry, these zwitterionic allylpalladium intermediates generally behave as three-carbon synthons to react with a multitude of acceptors to furnish the [3+*n*] cycloadditions, giving five,[3a,b,4a−i] six,[4j−n] seven,[3c,4o] and nine[3d]-membered carbo- and heterocyclic compounds (Scheme 1a,b). To the best of our knowledge, the TMM donor serving as a two-carbon synthon for palladium-catalyzed [3+2] cycloaddition has never been reported. We pondered that when Pd-methylene-TMM meets a dipole, the carbon−carbon double bond of Pd-methylene-TMM might work as a dipolarophile for 1,3-dipolar cycloaddition and the allylpalladium moiety will perform further allylation. As part of our continuing efforts with respect to cycloaddition reactions,[8] herein, we present the first palladium-catalyzed asymmetric tandem [3+2] cycloaddition/allylation of methylene-TMM to furnish biologically important functionalized chiral hexahydropyrazolo[5,1-*a*]isoquinoline derivatives (Scheme 1c).

Scheme 1. Palladium-Catalyzed Cycloaddition Reactions of TMM



To test the feasibility of the tandem reaction, we investigated the model reaction of methylene-TMM donor **1a** and azomethine imine **2a** in dichloromethane at room temperature (Table 1). To our delight, under catalysis of $Pd(PPh_3)_4$, the desired tandem reaction proceeded smoothly to deliver the racemic product in 71% yield with a 9:1 *E*:*Z* ratio (entry 1). Several axially chiral phosphoramidite ligands were then

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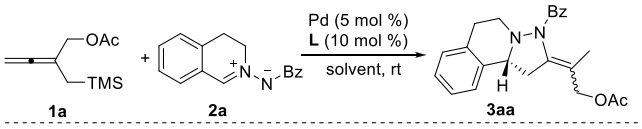
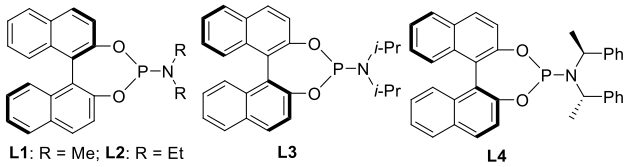
Table 1. Optimization of the Reaction Conditions[a]





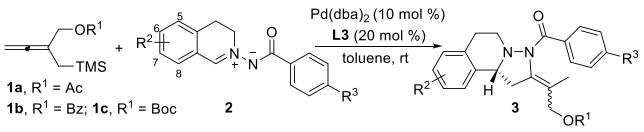
entry	L*x*	solvent	*t* (h)	yield (%)[b]	*E*:*Z*[c]	ee (%)[d]
1[e]	–	CH_2Cl_2	7	71	9:1	–
2	**L1**	CH_2Cl_2	48	NR[f]	–	–
3	**L2**	CH_2Cl_2	48	NR[f]	–	–
4	**L3**	CH_2Cl_2	12	92	9:1	81:97
5	**L4**	CH_2Cl_2	48	NR[f]	–	–
6	**L3**	DCE	24	76	3:1	79:80
7	**L3**	THF	24	trace	–	–
8	**L3**	toluene	14	90	3:1	87:95
9	**L3**	CH_3CN	12	86	2.3:1	81:99
10[e]	**L3**	toluene	20	72	3:1	85:97
11[g]	**L3**	toluene	12	99	3:1	91:97

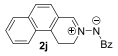
[a]Unless otherwise indicated, all reactions were performed with **1a** (0.15 mmol) and **2a** (0.10 mmol) in the presence of $Pd(dba)_2$ (5 mol %) and chiral ligand (10 mol %) in 1 mL of solvent. [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Determined by HPLC analysis using a chiral stationary phase. [e]$Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$ were used in entries 1 and 10, respectively. [f]No reaction. [g]Using 10 mol % $Pd(dba)_2$ and 20 mol % ligand.

examined (entries 2−5). Interestingly, chiral ligand **L3** was the only one that promoted the reaction (entry 4). Under catalysis of $Pd(dba)_2$ and axially chiral phosphoramidite ligand **L3**, the desired product was obtained in 92% yield with 81%:97% ee and a 9:1 *E*:*Z* ratio (entry 4). A quick screening of several solvents such as 1,2-dichloroethane (DCE), THF, toluene, and CH_3CN (entries 8−11, respectively) revealed that toluene is the optimal solvent, leading to product **3aa** in 90% yield with an 87%:95% ee and a 3:1 *E*:*Z* ratio (entry 8). $Pd_2(dba)_3{\cdot}CHCl_3$ also facilitated the reaction, but it did not aid in impairing the activity (entry 10). Increasing the loading of the catalyst [using 10 mol % $Pd(dba)_2$ and 20 mol % chiral ligand **L3**] increased both the yield and the enantioselectivity (entry 13). On the basis of the screening results presented above, the optimal reaction conditions were determined using $Pd(dba)_2$ (10 mol %) and chiral ligand **L3** (20 mol %) as the catalyst in toluene at rt. To investigate the practicality of the process, a large-scale reaction was conducted. In the presence of 10 mol % $Pd(dba)_2$ and 20 mol % **L3**, the reaction of **2a** (2.0 mmol) with **1a** (3.0 mmol) was performed for 15 h, providing 0.65 g of **3aa** (92% yield) with a 91%:97% ee and a 3:1 *E*:*Z* ratio.

After the optimized conditions had been established, various azomethine imines **2** were investigated in the tandem reaction (Table 2). The leaving group (R^1) of methylene-TMM donors **1** was first explored. When using acetyl or benzoyl as the leaving group, azomethine imine **2a** was completely converted, giving the corresponding products **3aa** and **3ba** in good to excellent yields and enantioselectivities (entries 1 and 2, respectively). In comparison, Boc-protected donor **1c** showed no reactivity (entry 3). With acetyl-protected donor **1a** as the substrate, various azomethine imines with different substituents, including

Table 2. Palladium-Catalyzed Tandem [3+2] Cycloaddition/ Allylation of Methylene-TMM[a]



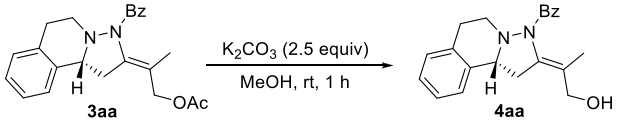
entry	1	2, R^2, R^3	t (h)	3	yield (%)[b]	*E*/*Z*[c]	ee (%)[d]
1	**1a**	**2a**, H, H	12	**3aa**	99	3:1	91/97
2	**1b**	**2a**, H, H	12	**3ba**	80	5:1	88/95
3	**1c**	**2a**, H, H	48	**3ca**	NR[e]	-	-
4	**1a**	**2b**, 7-F, H	16	**3ab**	82	4:1	94/99
5	**1a**	**2c**, 5-Cl, H	16	**3ac**	76	3.4:1	93/98
6	**1a**	**2d**, 6-Cl, H	18	**3ad**	95	2.5:1	91/99
7	**1a**	**2e**, 5-Br, H	12	**3ae**	81	3:1	91/91
8	**1a**	**2f**, 6-Br, H	12	**3af**	97	2.5:1	91/98
9	**1a**	**2g**, 7-Br, H	18	**3ag**	80	4:1	96/94
10	**1a**	**2h**, 5-Me, H	14	**3ah**	99	3.3:1	86/97
11	**1a**	**2i**, 7-Me, H	12	**3ai**	90	2.5:1	88/98
12	**1a**		18	**3aj**	72	3:1	91/97
13	**1a**	**2k**, H, F	16	**3ak**	92	3.5:1	82/89
14	**1a**	**2l**, H, Cl	16	**3al**	98	2.4:1	75/86
15	**1a**	**2m**, H, Me	14	**3am**	67	3:1	87/97
16	**1a**	**2n**, H, MeO	14	**3an**	75	3:1	83/96
17	**1a**	**2o**, H, CF_3	14	**3ao**	78	2:1	87/94

[a]Unless otherwise indicated, all reactions were carried out with **1** (0.15 mmol) and **2** (0.10 mmol) in 1 mL of toluene. [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Determined by HPLC analysis using a chiral stationary phase. [e]No reaction.

electron-neutral, electron-donating, and electron-withdrawing groups, were well tolerated, providing the desired products in high yields with good to excellent enantioselectivities (entries 4−12). Azomethine imines with a methyl substituent on the aromatic ring provided yields relatively higher than that with a halogen substituent (entries 10 and 11 vs entries 4−9). Different substituents at position 4 of the phenyl ring of the benzoyl protecting group had some effect on the reactivities and enantioselectivities (entries 13−17). The major isomer of product **3** was unambiguously assigned to be the *E*-isomer according to X-ray crystallographic data of product **3ac**.[9]

During exploration of further transformations of the products, we observed that the hydroxylation of product **3aa** proceeded well in the presence of K_2CO_3, affording only *E*-isomer **4aa** in 85% yield without any loss of the enantiomeric excess (Scheme 2). Encouraged by this result, we moved to investigate a one-pot

Scheme 2. Hydroxylation of Product 3aa



3:1 *E*/*Z*, 91%/97% ee — 85% yield, 91%ee, > 20:1 *E*/*Z*

sequential tandem reaction/hydroxylation procedure to synthesize allyl alcohol derivatives **4**. Using the established reaction system, Pd-catalyzed tandem reaction of methylene-TMM donor **1a** and azomethine imines **2** was performed for the given period of time, and then K_2CO_3 and MeOH were added to the flask to promote the hydroxylation. As shown in Table 3, a variety of azomethine imines were examined. All of these 1,3-

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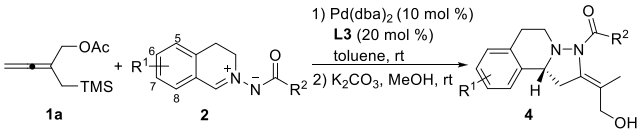
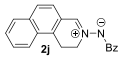
Table 3. One-Pot Synthesis of Allyl Alcohol Derivatives 4[a]



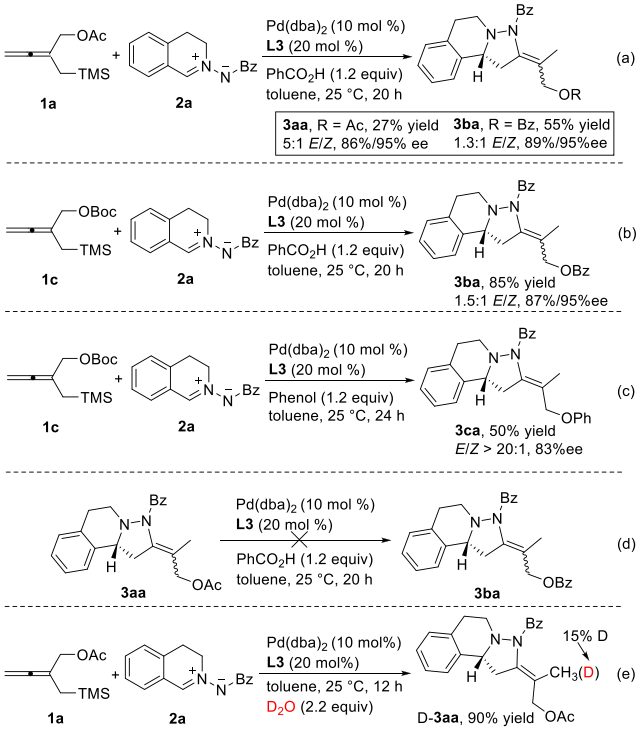
entry	2, R^1, R^2	t_1/t_2 (h)	4	yield (%)[b]	ee (%)[c]
1	**2a**, H, Ph	12/1.8	**4aa**	82	92
2	**2c**, 5-Cl, Ph	16/2	**4ac**	67	93
3	**2g**, 7-Br, Ph	18/2	**4ag**	82	95
4	**2h**, 5-Me, Ph	15/2.3	**4ah**	69	91
5	**2i**, 7-Me, Ph	12/2.1	**4ai**	80	91
6		20/2	**4aj**	84	90
7	**2k**, H, 4-FC_6H_4	18/2	**4ak**	74	87
8	**2m**, H, 4-MeC_6H_4	16/2	**4am**	68	86

[a]Unless otherwise indicated, all reactions were carried out with **1a** (0.15 mmol) and **2** (0.10 mmol) in 1 mL of toluene. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.

dipoles bearing electron-donating and -withdrawing substituents on the benzene ring or the benzoyl group worked well, leading to products **3c**–**3f** in good yields with good to excellent enantioselectivities (entries 1–8).

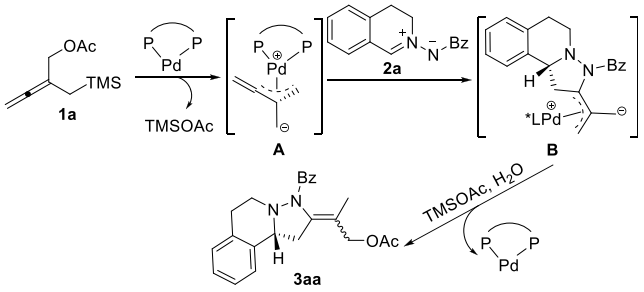
To gain some insights into the mechanism of this cycloaddition reaction, several control experiments were performed. When 1.2 equiv of benzoic acid was added to the model reaction mixture, the reaction of methylene-TMM donor **1a** and azomethine imine **2a** produced the anticipated product **3aa** in 27% yield and a new product **3ba** in 55% yield, in which the acetyl group of **3aa** was replaced by a benzoyl group (Scheme 3a). When Boc-protected methylene-TMM donor **1c** was used instead of Ac-protected donor **1a**, in the presence of benzoic acid, product **3ba** was produced in 85% yield (Scheme 3b). In the reaction of **1c**, when phenol was employed in the place of benzoic acid, a phenoxy ether **3ca** was afforded as the tandem reaction product in 50% yield (Scheme 3c). Treatment of product **3aa** with benzoic acid under standard conditions did not give product **3ba** (Scheme 3d). In addition, when 2.2 equiv of D_2O was added to the model reaction mixture, it could afford deuterated **3aa** in 90% yield with 15% D incorporation at the methyl group of propene that linked to alkenes (Scheme 3e). These results indicated that during palladium catalysis, an allylation reaction of Pd-methylene-TMM occurred during the reaction.

Scheme 3. Control Experiments



According to the control experimental results and some related reports,[7] as shown in Scheme 4, a plausible catalytic cycle was proposed. In the presence of a palladium catalyst, the methylene-substituted TMM donor was transformed into Pd-methylene-TMM complex **A** with simultaneous release of TMSOAc. Intermediate **A** undergoes cycloaddition with azomethine imine **2a**, affording intermediate **B**. Subsequent allylation of the acetyloxy anion gave product **3aa**.

Scheme 4. A Proposed Mechanism



In conclusion, palladium-catalyzed asymmetric tandem [3+2] cycloaddition/allylation of methylene-TMM has been achieved under mild reaction conditions to give the functionalized 1,2,3,5,6,10b-hexahydropyrazolo[5,1-*a*]isoquinoline derivatives in good to excellent yields with good to excellent enantioselectivities. This is the first example of asymmetric tandem [3+2] cycloaddition/allylation reaction of Pd-methylene-TMM. The insecticidal and bactericidal activities of all novel compounds synthesized by our methodology are being evaluated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01064.

Experimental procedure, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1898870 and 1898872–1898873 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hchguo@cau.edu.cn.

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ORCID

Hongchao Guo: 0000-0002-7356-4283

Notes

The authors declare no competing financial interest.

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