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Pd/C-Catalyzed Dehydrogenative [3 + 2] Cycloaddition for the Synthesis of Functionalized Tropanes

Hai-Jun Wang,[a] Lei Guo,[a] Cheng-Feng Zhu,[a] Yun-Fei Luo,[a] You-Gui Li,[a] and Xiang Wu*[a]

Abstract: A Pd/C-catalyzed cascade approach for the synthesis of attractive benzo-fused tropanes was developed. The reaction proceeds through a sequential Pd/C-catalyzed dehydrogenative formation of azomethine ylides from amines and 1,3-dipolar cycloaddition. It allows the generation of structurally complex benzo-fused tropanes in good yields with excellent diastereoselectivities under mild reaction conditions. Preliminary results of asymmetric version of the reaction reveal that the copper catalyst and chiral monophosphoramidite ligand can furnish optically active products with moderate ee.

Introduction

[3 + 2]-Cycloaddition reactions are powerful tools for the synthesis of hetero-atoms containing five-membered cyclic molecules.[1] Among them, azomethine ylides are commonly nitrogen-based 1,3-dipoles which represent multifunctional synthons to generate pyrrolidine or pyrroline derivatives when reacting with unsaturated carbon−carbon bonds.[2] Moreover, azomethine ylides have high utility in the synthesis of bioactive heterocycles and complex natural products.[2f,2g] Usually, azomethine ylides are unstable and have to be generated *in situ* from imines, iminium salts, aziridines and silylonium ions.[2a,2b] Recently, a few new oxidative processes, including photoredox catalysis,[3] indirect oxidation by oxygen or peroxide species[4] and metal catalyzed dehydrogenation,[5] have been developed for converting amines to azomethine ylide intermediates. Although these azomethine ylide intermediates have been successfully used in the oxidative [3 + 2] cycloadditions, and important progress has been made in the last decade, there still remains a great challenge for the synthesis of interesting and important structural moieties with high efficiency and selectivity.

Benzo-fused tropanes, containing phenyl rings and tropane moieties, exhibit a wide range of biological activities. Compound **1** is an antitumor drug candidate[6] and compound **2** has been studied for the treatment of Type 2 diabetes[7] (Figure 1). MK-801, the tropane core fused with two benzene rings, displays anticonvulsant activity and gives it potential as a drug to treat CNS disorders.[8]

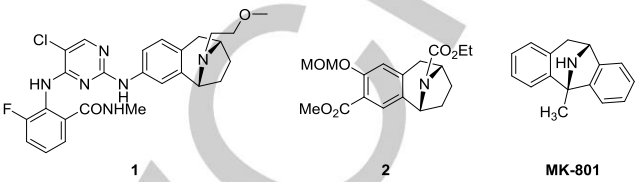
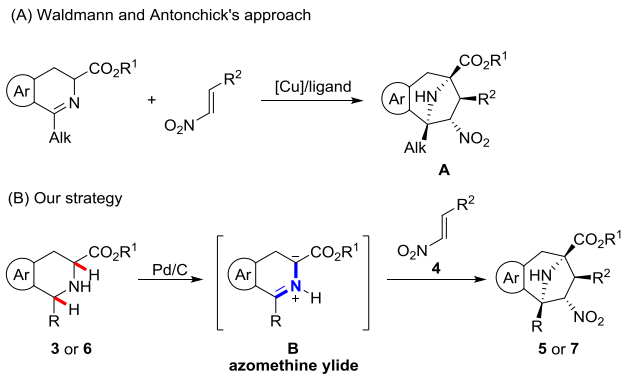


Figure 1. Representative benzo-fused tropanes with biological activities.

However, only a few routes have been disclosed for the synthesis of benzo-fused tropane scaffolds.[5c,9] Among these approaches, [3 + 2] cycloaddition is an efficient strategy for the construction of benzo-fused tropane derivatives.[5c,9b,9g,9h,9k,9l,9n,9o] Recently, Waldmann, Antonchick and co-workers developed a direct and efficient copper-catalyzed and classical 1,3-dipolar cycloaddition reaction of 1,3-fused cyclic azomethine ylides and nitroalkenes for the synthesis of functionalized benzo-fused tropane scaffolds **A** with excellent diastereoselectivities and enantioselectivities, which have been found to be novel inhibitors of skin cancer (Scheme 1A).[9k] In comparison, the oxidative dehydrogenative [3 + 2] cycloaddition, a combination of two processes, including the metal catalyzed dehydrogenative generation of azomethine ylides and subsequent 1,3-dipolar cycloaddition, results in the concomitant formation of two C–C bonds via direct oxidative functionalization of C–H bonds and is characterized by a high degree of step economy and operational efficiency.[5c] Therefore, since we are interested in the oxidative



Scheme 1. Strategic Accesses to Functionalized Benzo-fused Tropanes

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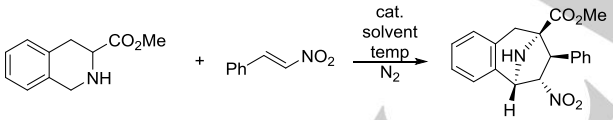
cycloadditions for the synthesis of structurally complex compounds,[10] we describe herein a Pd/C-catalyzed dehydrogenative formation of azomethine ylides **B** from amines and subsequent [3 + 2] cycloaddition for the synthesis of benzo-fused tropanes (Scheme 1B). Moreover, a promising asymmetric process using a chiral BINOL-based phosphoramidite as ligand was developed to provide highly valuable chiral tropane derivatives.

Results and Discussion

Initially, phenylalanine derivative **3a** was employed as the dipole precursor and *trans*-β-nitrostyrene **4a** as the dipolarophile in the dehydrogenative [3 + 2] cycloaddition. Palladium black was first utilized to catalyze the generation of azomethine ylides from **3a** in toluene at 110 °C. The desired tropane product **5aa** was isolated in 29% yield with complete diastereomeric control (dr > 20:1) (Table 1, entry 1). Intriguingly, when Pd/C was used as a replacement for palladium black, the yield was increased to 52% (entry 2). Then, a series of temperatures were evaluated for the reaction and 70 °C was found to be the most suitable operation temperature (entries 2-7). Moreover, several metal catalysts such as Ru/C, Rh/C and Pt/C were also screened, and a satisfactory yield of 76% was obtained using Pd/C as the catalyst (entries 4, 8-10). A final evaluation of solvents showed that toluene is the most suitable media to allow the reaction and gives the highest yield (entries 4 and 12-14).

Table 1. Optimization of the Reaction Conditions[a]



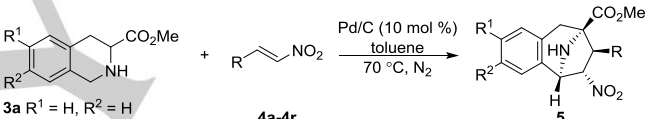
3a **4a** **5aa**

entry	cat.	solvent	temp (°C)	yield (%)[b]
1	Pd black	toluene	110	29
2	Pd/C	toluene	110	52
3	Pd/C	toluene	90	55
4	Pd/C	toluene	70	76
5	Pd/C	toluene	60	69
6	Pd/C	toluene	50	40
7	Pd/C	toluene	rt	0
8	Ru/C	toluene	70	42
9	Rh/C	toluene	70	40
10	Pt/C	toluene	70	37
11	Pd/C	MeCN	70	63
12	Pd/C	$CHCl_3$	70	30
13	Pd/C	EtOAc	70	65
14	Pd/C	THF	70	75

[a]The reaction was carried out with **3a** (0.1 mmol) and **4a** (2.0 equiv) in the presence of 10 mol % of metal catalysts under N_2. The resulting solution was stirred for 36 h. [b]Yield of the isolated product. Racemic **5aa** was obtained.

With the optimal reaction conditions in hand, we next surveyed the scope for both substrates **3** and **4**. A variety of nitrostyrenes **4a−r** with different substituents on the phenyl ring were treated with methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3a**) in the reactions (Table 2, entries 1-14). Electron-neutral, electron-donating and electron-withdrawing substituents were generally well-tolerated, affording **5ab−ao** in good yields and with excellent diastereoselectivity all dr > 20:1). Particularly, due to steric hindrance, *meta*- and *para*-substituents resulted in considerably higher yields than those of *ortho*-substituents (entries 2 and 3 vs 1, entries 5 and 6 vs 4). Additionally, 1,2,3,4,5-pentafluoro phenyl-substituted substrate **4o** gave the product **5ao** smoothly, albeit in a relatively lower yield (entry 14). 2-Naphthyl-substituted nitroethene **4p** also afford the corresponding product **5ap** in good yield (entry 15). Notably, the furan- and thiophene-derived heteroaromatic nitroalkenes reacted well to give the products **5aq** and **5ar** (entries 16 and 17). Moreover, electron-rich (methoxyl) group substituted tetrahydroisoquinolines **3b** and **3c** smoothly underwent the cascade dehydrogenation/cycloaddition to furnish the corresponding products in moderate yields (entries 18 and 19).

Table 2. Scope of tetrahydroisoquinolines **3** and nitroalkenes **4**[a]



3a R^1 = H, R^2 = H
3b R^1 = MeO, R^2 = H
3c R^1 = MeO, R^2 = MeO

4a-4r **5**

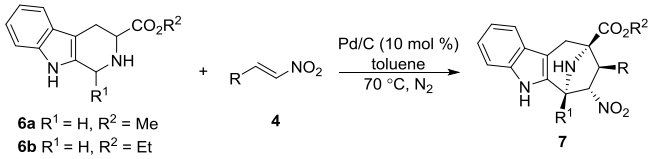
entry	**3**	R	**4**	**5**	yield (%)
1	**3a**	2-MeC_6H_4	**4b**	**5ab**	60
2	**3a**	3-MeC_6H_4	**4c**	**5ac**	79
3	**3a**	4-MeC_6H_4	**4d**	**5ad**	71
4	**3a**	2-$NO_2C_6H_4$	**4e**	**5ae**	70
5	**3a**	3-$NO_2C_6H_4$	**4f**	**5af**	78
6	**3a**	4-$NO_2C_6H_4$	**4g**	**5ag**	76
7	**3a**	4-CNC_6H_4	**4h**	**5ah**	83
8	**3a**	4-$CF_3C_6H_4$	**4i**	**5ai**	78
9	**3a**	4-ClC_6H_4	**4j**	**5aj**	80
10	**3a**	4-$MeOC_6H_4$	**4k**	**5ak**	76
11	**3a**	4-FC_6H_4	**4l**	**5al**	81
12	**3a**	2,3-$Cl_2C_6H_3$	**4m**	**5am**	81
13	**3a**	3,4-$(MeO)_2C_6H_3$	**4n**	**5an**	80
14	**3a**	2,3,4,5,6-F_5C_6	**4o**	**5ao**	61
15	**3a**	2-naphthyl	**4p**	**5ap**	76
16	**3a**	2-furyl	**4q**	**5aq**	70
17	**3a**	2-thienyl	**4r**	**5ar**	58
18	**3b**	C_6H_5	**4a**	**5ba**	49
19	**3c**	C_6H_5	**4a**	**5ca**	45

[a]The reaction was carried out with **3** (0.1 mmol) and **4** (2.0 equiv) in the presence of 10 mol % of Pd/C in toluene (1 mL) under N_2 at 70 °C for 36 h. dr > 20:1. Racemic **5** were obtained.

To explore the scope of this transformation further, we employed tetrahydrocarbolines **6a**-**6e** as the dipole precursors. First, **6a** was treated with nitrostyrenes **4** that had a variety of substituting groups on the phenyl ring with different electronic properties. The results showed that the variation has little evident effect on the reaction outcomes (76%-90% yields, Table 2, entries 1-11). The phenyl substituent of substrate **4** could be replaced with furan and thiophene, leading to the products **7aq**

and **7ar** in good yields (entries 12, 13). However, 3-indolyl nitroethene showed lower reactivity to afford the desired product **7as** in a lower yield of 26% (entry 14). Moreover, ethyl ester **6b** was also examined, providing a good yield (entry 15). When the hydrogen atom at the C1 position of 3,4-dihydro-β-carboline was changed to a methyl (**6c** and **6d**) or phenyl (**6e**) group, the yields of the reaction were reduced slightly, but essentially only a single diastereomer (**7ca**, **7da**[11] and **7ea**) was formed (entries 16-18). Unfortunately, less reactive alkyl nitroalkenes such as cyclohexyl- and benzyl β-substituted nitroethenes could not give any products (See Supporting Information).

Table 3. Scope of tetrahydrocarbolines **6** and nitroalkenes **4a**[a]

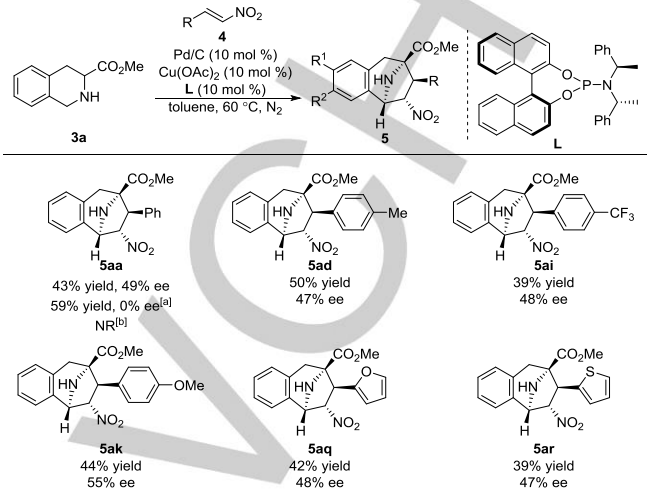


6a R^1 = H, R^2 = Me
6b R^1 = H, R^2 = Et
6c R^1 = Me, R^2 = Me
6d R^1 = Me, R^2 = Et
6e R^1 = Ph, R^2 = Me

entry	6	R	4	7	yield (%)[b]
1	**6a**	C_6H_5	**4a**	**7aa**	86
2	**6a**	4-MeC_6H_4	**4d**	**7ad**	90
3	**6a**	4-$NO_2C_6H_4$	**4g**	**7ag**	83
4	**6a**	4-CNC_6H_4	**4h**	**7ah**	86
5	**6a**	4-$CF_3C_6H_4$	**4i**	**7ai**	76
6	**6a**	4-ClC_6H_4	**4j**	**7aj**	88
7	**6a**	4-FC_6H_4	**4l**	**7al**	86
8	**6a**	2,3-$Cl_2C_6H_3$	**4m**	**7am**	78
9	**6a**	3,4-$(MeO)_2C_6H_3$	**4n**	**7an**	85
10	**6a**	2,3,4,5,6-F_5C_6	**4o**	**7ao**	79
11	**6a**	2-naphthyl	**4p**	**7ap**	87
12	**6a**	2-furyl	**4q**	**7aq**	81
13	**6a**	2-thienyl	**4r**	**7ar**	84
14	**6a**	3-indolyl	**4s**	**7as**	26
15	**6b**	C_6H_5	**4a**	**7ba**	76
16	**6c**	C_6H_5	**4a**	**7ca**	63
17	**6d**	C_6H_5	**4a**	**7da**	54
18	**6e**	C_6H_5	**4a**	**7ea**	49

[a]The reaction was carried out with **6** (0.1 mmol) and **4** (2.0 equiv) in the presence of 10 mol % of Pd/C in toluene (1 mL) under N_2 at 70 °C for 36 h. dr > 20:1. Racemic **7** were obtained.

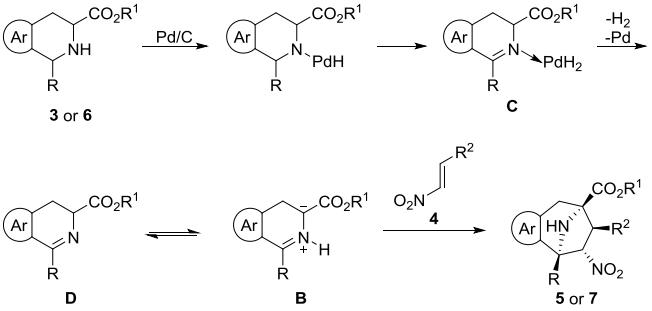
Finally, an attempt for an asymmetric cascade via palladium catalyzed dehydrogenation/copper catalyzed dipolar cycloaddition was conducted. Several commercially available chiral phosphine ligands were screened (for details, see Supporting Information), in which the chiral monophosphoramidite ligand (*S*,*R*,*R*)-**L** displayed the best reactivity and provided the best (but moderate) enantioselectivities for products in moderate yields when the reaction proceeded at 60 °C using copper acetate as the catalyst (Scheme 2). Regardless of the electronic character of the substituents on the phenyl ring of nitrostyrenes **4** and heteroaromatic nitroalkenes **4**, reactions proceeded smoothly, and products with moderate ee were obtained.[12] In the case of the product **5aa**, chiral benzo-fused tropane containing four contiguous chiral centers was attained with 49% ee. Interestingly, when the reaction proceeded at 70 °C, no enantioselectivity was observed while at 50 °C the reaction did not take place (Scheme 2).



Scheme 2. Preliminary Asymmetric Studies. Reaction conditions: **3a** (0.1 mmol), **4** (0.2 mmol), Pd/C(0.01 mmol), $Cu(OAc)_2$ (0.01 mmol), **L** (0.01 mmol) in toluene (1 mL) under N_2 at 60 °C for 80 h. dr > 20:1. [a]The reaction was carried out at 70 °C. [b]The reaction was carried out at 50 °C. NR = No Reaction. Optical active compounds **5** were obtained.

On the basis of the experimental results above and previous reports,[13] we proposed here a plausible reaction mechanism for the palladium-catalyzed dehydrogenative [3 + 2] cycloaddition (Scheme 3). Palladium catalysts have long been known to catalyze dehydrogenation of secondary amines to imines.[14] Initially, palladium inserts into the N–H bond followed by β-H elimination to generate the imine complex **C**. Then, the corresponding cyclic imines **D** convert to azomethine ylides **B** by 1,2-prototropy. Finally, the 1,3-dipolar cycloaddition occurs smoothly to afford tropane derivatives when the intermediates **B** are treated with nitroalkenes **4**.

Scheme 3. Plausible Reaction Mechanism



Conclusions

In summary, we have developed a Pd/C-catalyzed dehydrogenative [3 + 2] cycloaddition for the synthesis of benzo-

fused tropanes. The reaction proceeds through a sequential Pd/C-catalyzed dehydrogenative formation of azomethine ylides from amines and 1,3-dipolar cycloaddition. It allows the generation of structurally complex benzo-fused tropanes in good yields with excellent diastereoselectivities under mild reaction conditions. Moreover, preliminary results of the asymmetric version of the reaction reveal that the copper catalyst and chiral monophosphoramidite ligand can furnish optically active products with moderate ee.

Experimental Section

General procedure for the synthesis of tropanes 5 or 7. Esters **3** or **6** (0.1 mmol), nitroalkenes **4** (30 mg, 0.2 mmol) and Pd/C (10.6 mg, 0.01 m mol) were added in an oven-dried Schlenk tube. The tube was then seale d, evacuated, and backfilled with nitrogen using standard Schlenk techni que. Toluene (1 mL) was sequentially added by syringe at ambient temp erature. The resulting mixture was heated to 70 °C (oil bath) for 36 hours. Solvents were evaporated under reduced pressure. The residue was dir ected purified by column chromatography on silica gel to afford the comp ound **5** or **7.**

Acknowledgements

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Keywords: Palladium • Dehydrogenative • [3 + 2] Cycloaddition • Tropanes • Asymmetric

[1] a) A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, John Wiley & Sons, Inc., New York, **2002**; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366-5412; c) M. S. Singh, S. Chowdhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603-1644; d) Y. Wei, M. Shi, *Org. Chem. Front.* **2017**, *4*, 1876-1890.

[2] a) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765-2810; b) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484-4517; c) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296-1310; d) J. Adrio, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 12434-12446; e) A. Mendoza, J. Otero-Fraga, M. Montesinos-Magraner, *Synthesis* **2016**, *49*, 802-809; f) G. Pandey, D. Dey, S. K. Tiwari, *Tetrahedron Lett.* **2017**, *58*, 699-705; g) H. Döndas, M. de Gracia Retamosa, J. Sansano, *Synthesis* **2017**, *49*, 2819-2851; h) B. Bdiri, B.-J. Zhao, Z.-M. Zhou, *Tetrahedron: Asymmetry* **2017**, *28*, 876-899; i) X. Fang, C. J. Wang, *Org. Biomol. Chem.* **2018**, *16*, 2591-2601.

[3] a) Y. Q. Zou, L. Q. Lu, L. Fu, N. J. Chang, J. Rong, J. R. Chen, W. J. Xiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 7171-7175; *Angew*. *Chem*. **2011**, *123*, 7309-7313; b) M. Rueping, D. Leonori, T. Poisson, *Chem. Commun.* **2011**, *47*, 9615-9617; c) S. Guo, H. Zhang, L. Huang, Z. Guo, G. Xiong, J. Zhao, *Chem. Commun.* **2013**, *49*, 8689-8691; d) L. Huang, J. Zhao, *Chem. Commun.* **2013**, *49*, 3751-3753; e) C. Vila, J. Lau, M. Rueping, *Beilstein J Org Chem* **2014**, *10*, 1233-1238; f) D. Chandrasekhar, S. Borra, J. S. Kapure, G. S. Shivaji, G. Srinivasulu, R. A. Maurya, *Org. Chem. Front.* **2015**, *2*, 1308-1312; g) D. Chandrasekhar, S. Borra, J. B. Nanubolu, R. A. Maurya, *Org. Lett.* **2016**, *18*, 2974-2977; h) A. Fujiya, M. Tanaka, E. Yamaguchi, N. Tada, A. Itoh, *J. Org. Chem.* **2016**, *81*, 7262-7270.

[4] a) C. Yu, Y. Zhang, S. Zhang, H. Li, W. Wang, *Chem. Commun.* **2011**, *47*, 1036-1038; b) C. Feng, J.-H. Su, Y. Yan, F. Guo, Z. Wang, *Org. Biomol. Chem.* **2013**, *11*, 6691-6694; c) H. M. Huang, Y. J. Li, Q. Ye, W. B. Yu, L. Han, J. H. Jia, J. R. Gao, *J. Org. Chem.* **2014**, *79*, 1084-1092; d) H.-M. Huang, F. Huang, Y.-J. Li, J.-H. Jia, Q. Ye, L. Han, J.-R. Gao, *RSC Adv.* **2014**, *4*, 27250-27258; e) S. Nekkanti, N. P. Kumar, P. Sharma, A. Kamal, F. M. Nachtigall, O. Forero-Doria, L. S. Santos, N. Shankaraiah, *RSC Adv.* **2016**, *6*, 2671-2677; f) W. Wang, J. Sun, H. Hu, Y. Liu, *Org. Biomol. Chem.* **2018**, *16*, 1651-1658.

[5] a) R. Grigg, F. Heaney, *J. Chem. Soc., Perkin Trans. 1* **1989**, 198; b) R. Grigg, F. Heaney, J. Idle, A. Somasunderam, *Tetrahedron Lett.* **1990**, *31*, 2767-2770; c) R. Grigg, A. Somasunderam, V. Sridharan, A. Keep, *Synlett* **2009**, *2009*, 97-99; d) R. M. Gorman, M. A. Little, J. A. Morris, V. Sridharan, *Chem. Commun.* **2012**, *48*, 9537-9539; e) J. Windle, M. Allison, H. Shepherd, V. Sridharan, *RSC Adv.* **2014**, *4*, 2624-2627; f) M. Allison, V. Sridharan, *Tetrahedron Lett.* **2015**, *56*, 6551-6555; g) R. Lowe, S. Fathy, V. Sridharan, *Tetrahedron Lett.* **2017**, *58*, 2658-2660.

[6] G. Ahmed, A. Bohnstedt, H. J. Breslin, J. Burke, M. A. Curry, J. L. Diebold, B. Dorsey, B. J. Dugan, D. Feng, D. E. Gingrich, T. Guo, K.-K. Ho, K. S. Learn, J. G. Lisko, R.-Q. Liu, E. F. Mesaros, K. Milkiewicz, G. R. Ott, J. Parrish, J. P. Theroff, T. V. Thieu, R. Tripathy, T. L. Underiner, J. C.Wagner, L.Weinberg, G. J.Wells, M. You, C. A. Zificsak, PCT Int. Appl. WO 2008051547, 2008.

[7] J. Ammenn, M. Paal, G. Ruehter, T. Schotten, W. Stenzel, PCT Int. Appl. WO 2000078724, 2000.

[8] E. H. Wong, J. A. Kemp, T. Priestley, A. R. Knight, G. N. Woodruff, L. L. Iversen, *Proc. Natl. Acad. Sci. U. S. A.* **1986**, *83*, 7104-7108.

[9] a) G. L. Grunewald, D. J. Sall, J. A. Monn, *J. Med. Chem.* **1988**, *31*, 433-444; b) A. Padwa, D. C. Dean, M. H. Osterhout, L. Precedo, M. A. Semones, *J. Org. Chem.* **1994**, *59*, 5347-5357; c) K. P. Constable, B. E. Blough, F. I. Carroll, *Chem. Commun.* **1996**, 717-718; d) G. A. Molander, E. D. Dowdy, *J. Org. Chem.* **1999**, *64*, 6515-6517; e) M. Ikeda, M. Hamada, S. A. A. El Bialy, K. Matsui, S. Kawakami, Y. Nakano, S. M. M. Bayomi, T. Sato, *Heterocycles* **2000**, *52*, 571-574; f) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784-10785; g) H.-S. Yeom, J.-E. Lee, S. Shin, *Angew. Chem. Int. Ed.* **2008**, *47*, 7040-7043; *Angew*. *Chem*. **2008**, *120*, 7148-7151; h) S. Xing, W. Pan, C. Liu, J. Ren, Z. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 3215-3218; *Angew*. *Chem*. **2010**, *122*, 3283-3286; i) Q. Li, X. Jiang, C. Fu, S. Ma, *Org. Lett.* **2011**, *13*, 466-469; j) D. M. Schultz, J. P. Wolfe, *Org. Lett.* **2011**, *13*, 2962-2965; k) R. Narayan, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 12892-12896; *Angew*. *Chem*. **2013**, *125*, 13130-13134; l) J.-H. Xu, S.-C. Zheng, J.-W. Zhang, X.-Y. Liu, B. Tan, *Angew. Chem. Int. Ed.* **2016**, *55*, 11834-11839; *Angew. Chem*. **2016**, *128*, 12013-12018; m) K. H. V. Reddy, E. Yen-Pon, S. Cohen-Kaminsky, S. Messaoudi, M. Alami, *J. Org. Chem.* **2018**, *83*, 4264-4269. n) Sun, B.; Ren, J.; Xing, S.; Wang, Z. *Adv. Synth. Catal.* **2018**, *360*, 1529-1537; o) Zheng, X.; Yang, W.-L.; Liu, Y.-Z.; Wu, S.-X.; Deng, W.-P. *Adv. Synth. Catal.* **2018**, *360*, 2843-2853.

[10] a) X. Wu, D.-F. Chen, S.-S. Chen, Y.-F. Zhu, *Eur. J. Org. Chem.* **2015**, 468-473; b) Y. Yao, H.-J. Zhu, F. Li, C.-F. Zhu, Y.-F. Luo, X. Wu, E. A. B. Kantchev, *Adv. Synth. Catal.* **2017**, *359*, 3095-3101; c) X. Wu, H. J. Zhu, S. B. Zhao, S. S. Chen, Y. F. Luo, Y. G. Li, *Org. Lett.* **2018**, *20*, 32-35.

[11] The relative configuration of **7da** was assigned by comparison of chemical shifts and coupling constants with those of known compound reported by Waldmann, Antonchick and co-workers, see ref. 9k. The relative configurations of all other compounds were assigned by analogy.

[12] The absolute configuration of **5** was established according to the retention time in HPLC using chiral columns and comparison with the sequence of retention times obtained for the analogues reported by Waldmann, Antonchick and co-workers, see ref. 9k.

[13] a) S. Murahashi, T. Hirano, T. Yano, *J. Am. Chem. Soc.* **1978**, *100*, 348-350; b) S. Murahashi, T. Watanabe, *J. Am. Chem. Soc.* **1979**, *101*, 7429-7430; c) S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443-2465; *Angew. Chem*. **1995**, *107*, 2670-2693.

[14] a) J. Muzart, *J. Mol. Catal. A: Chem.* **2009**, *308*, 15-24; b) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681-703.

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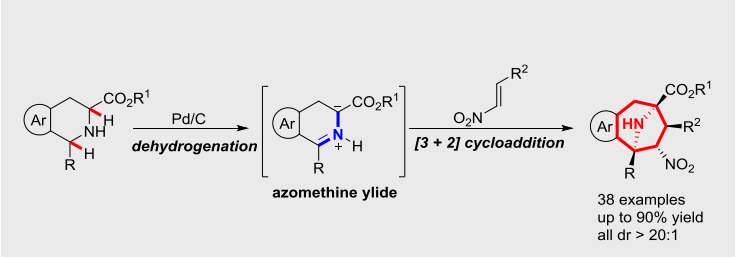

Heterocyclic Chemistry

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Pd/C-Catalyzed Dehydrogenative [3 + 2] Cycloaddition for the Synthesis of Functionalized Tropanes

Described is a Pd/C-catalyzed dehydrogenative [3 + 2] cycloaddition for the synthesis of benzo-fused tropanes. The reaction proceeds through a sequential Pd/C-catalyzed dehydrogenative formation of azomethine ylides from amines and 1,3-dipolar cycloaddition.