ORGANIC LETTERS

2007
Vol. 9, No. 24
5063−5066

Organocatalyzed Cyclizations of π-Allylpalladium Complexes: A New Method for the Construction of Five- and Six-Membered Rings

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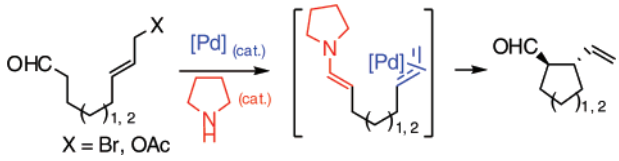
Received September 27, 2007

ABSTRACT



Synergic combination of organotransition metal catalysis and organocatalysis allows, for the first time, the Tsuji–Trost cyclization of aldehydes. A catalytic asymmetric variant of the reaction is also possible.

Allylation of soft carbon nucleophiles with π-allylpalladium species, also known as the Tsuji−Trost reaction, is an important method of carbon−carbon bond formation.[1] The reaction is performed under mild conditions, regioselectively, with a wide tolerance of functional groups.[2] An intramolecular variant of the reaction is also successful, giving rise to rings of various sizes. Catalytic asymmetric variants are known at both inter- and intramolecular reactions, usually with high levels of asymmetric induction.[3] However, the reaction has one serious limitation, as it only works well with strongly (i.e., with doubly) stabilized enolates, whereas synthetically more attractive proenolates, such as ketones or esters, cannot be used. Hard nucleophiles, organometallics, also react with allylpalladium species but by a different mechanism, with a different stereochemical outcome and with reduced tolerance of functional groups. The efforts invested to overcome this restriction met with success at the intermolecular level. This issue has been recently reviewed and involves the use of novel ligands, iridium-based catalysts, additives, or in situ formation of enolates from the corresponding allyl enol carbonates and allyl β-keto esters.[4] However, contrary to the plethora of examples of cyclization of stabilized enolates, intramolecular allylations of ordinary enolates are not known. To the best of our knowledge, a single exception is the cyclization of a nitro derivative;[5] however, this example is rather specific, as the nitro group is the strongest electron-withdrawing group in organic chemistry and the acidity of of the α-hydrogen ($pK_a = 9$) is

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(1) (a) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197. (b) Trost, B. *Pure Appl. Chem.* **1981**, *53*, 2357.

(2) For comprehensive reviews, see: (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed., de Meijere, A., Assoc. Ed.; J. Wiley & Sons: New York, 2002; Vol. 2, Chapter V, p 1669. (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, p 799.

(3) For review articles on catalytic asymmetric allylation with π-allyl palladium complexes, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 2000; p 833. (c) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 593. (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

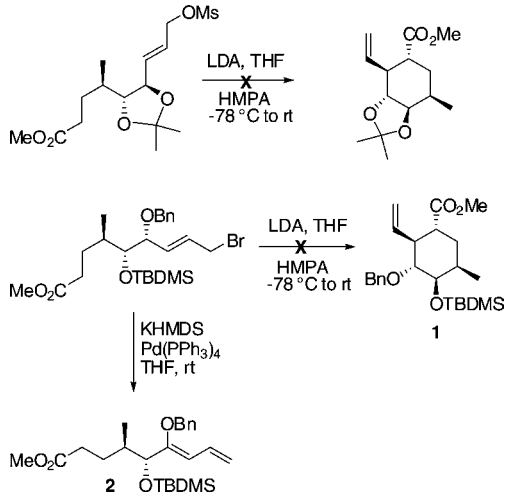
(4) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952 and references therein.

(5) Kardos, N.; Genet, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 1525.

10.1021/ol7023554 CCC: $37.00
Published on Web 10/24/2007

similar to that of doubly activated compounds.[6] The importance of this transformation is further stressed by the fact that intramolecular allylation of ester and ketone enolates can be a surprisingly difficult reaction. In the whole chemical literature we were able to find only four examples of intramolecular allylations of ester,[7] ketone,[8] or amide enolates.[9] In the course of a project directed toward the total synthesis of the antibiotic abyssomicin,[10] we needed a method for the efficient vinylcyclohexane ring-closure from the corresponding proenolate. Several attempts to accomplish this transformation under conventional experimental conditions, as delineated in Scheme 1, (KHMDS, THF, with or without

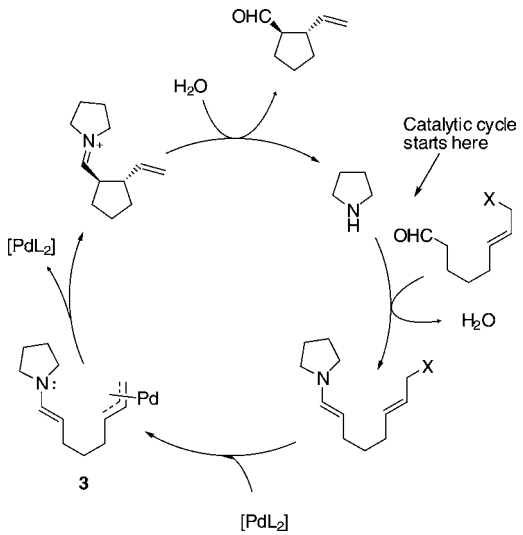
Scheme 1. Attempted Intramolecular Allylation of Esters



HMPA, −78 °C to 50 °C) failed, with the substrates either not reacting or decomposing under more energetic reaction conditions. In order to enhance the reactivity of the allylic part of the molecule, the reaction was performed in the presence of a catalytic amount of $Pd(PPh_3)_4$; in this case a smooth reaction occurred; however, the product was not the cyclohexane derivative **1**, but the corresponding diene **2**. Not surprisingly, the ester enolate behaved more as a base than as a nucleophile, promoting the elimination of HBr from the π-allyl palladium species.[11]

Thus, softer nucleophiles were required, and we turned our attention toward enamines, whose use in intermolecular reactions with π-allyl palladium species has literature precedents.[12] However, instead of preparing the corresponding enamine separately, which would be inconvenient and of limited synthetic value, we designed a catalytic cycle, as represented in Scheme 2, which would create in situ the

Scheme 2. Mechanism of the [Pd]/Amine Cocatalyzed Cyclization



required reactive intermediates. The salient feature of this concept is the combination of organocatalysis[13] and organo-transition metal catalysis. The issue of our concern was the fact that both catalysts (Pd and amine) must operate on the same molecule; given the reversible nature of all steps and substoichiometric quantities of the catalysts, the question was whether the active intermediate **3**—enamine of the π-allyl palladium complex—would be present in sufficiently high concentration to secure an efficient synthetic transformation. The feasibility of the envisaged protocol was tested in the reaction of **4** with catalytic amounts of $Pd(PPh_3)_4$, pyrrolidine, and one equivalent of triethylamine, in THF as a solvent, at rt (conditions A). Much to our delight, a rapid reaction took place, giving rise to 2-vinyl-cyclopentanecarbaldehyde **12**, which was isolated in 72% yield (Table 1, entry 1). The cyclization was stereoselective, with the ratio of diastereoisomers *trans:cis* = 11:1. No reaction took place in the absence of any of the two catalysts, thus confirming the proposed mechanism. While this research was underway, Cordova reported a similar approach to the intermolecular allylation of carbonyl compounds, using allyl acetate as the electrophile, in DMSO as a solvent.[14] We found these conditions also suitable for cyclizations, which occurred with comparable yields (conditions B, entry 2). Regioisomeric,

(6) House, H., O. *Modern Synthetic Reactions*, 2nd ed.; The Benjamin/Cummins Publishing Company: Menlo Park, 1972; p 494.

(7) Kim, D.; Lim, J. I.; Shin, K. J.; Kim, H. S. *Tetrahedron Lett.* **1993**, *34*, 6557.

(8) Watanabe, K.; Suzuki, J.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.

(9) (a) Jo, H.; Li, J.; Kim, H.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 7043. (b) Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*, 1433.

(10) Unpublished results. For the isolation and structure elucidation of abyssomicin, see: Bister, B.; Bishoff, D.; Strobele, M.; Riedlinger, J.; Reicke, A.; Wolter, F.; Bull, A. T.; Zahner, H.; Fiedler, H. P.; Sussmuth, R. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2574.

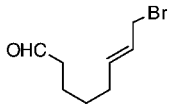
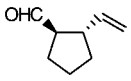
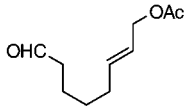
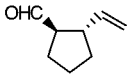
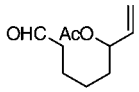
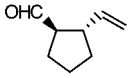
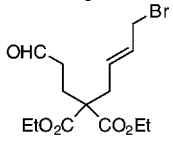
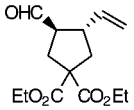
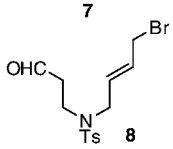
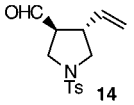
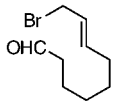
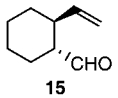
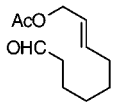
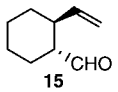
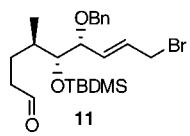
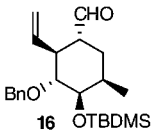
(11) A review article on eliminations of π-allyl palladium derivatives: I. Shimizu, in ref 2a), p 1981.

(12) (a) Hiroi, K.; Abe, J.; Suya, K.; Sato, S.; Koyama, T. *J. Org. Chem.* **1994**, *59*, 203. (b) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720.

(13) (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley: Weinheim, 2005. For review articles on organocatalysis, see: (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (d) The 8th issue of *Acc. Chem. Res.* **2004**, *37*, several reviews on organocatalysis.

(14) Ibrahem, I.; Cordova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952.

Table 1. [Pd]/pyrrolidine-Cocatalyzed Cyclizations of Aldehydes

entry	reactant	method[a]	product	yield[b] *trans/cis*
1	 **4**	A	 **12**	72%[c] *11/1*
2	 **5**	B	 **12**	63%[c] *10/1*
3	 **6**	B	 **12**	53% *2/1*
4	 **7**	A	 **13**	75% *13/1*
5	 **8**	A	 **14**	80% *10/1*
6	 **9**	A	 **15**	60% *7/1*
7	 **10**	B	 **15**	65% *10/1*
8	 **11**	A	 **16**	95%[d] *7/1*

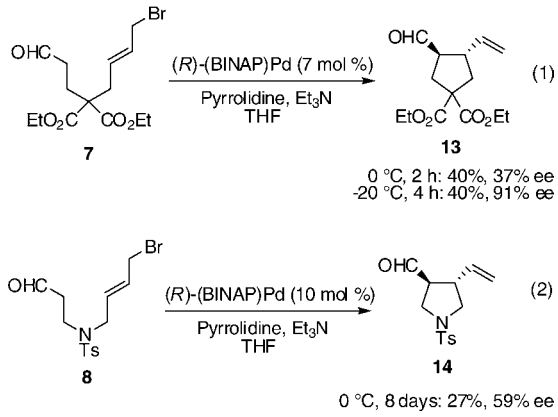
[a] Method A: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), Et_3N (1 equiv), THF, rt, 30 min. Method B: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), DMSO, rt, 30 min. [b] Yield of the isolated, pure compound. [c] Isolated as the corresponding alcohol, after the reduction with $NaBH_4$. [d] 10 mol % of $Pd(PPh_3)_4$.

secondary allylic acetate **6** gave the same product **12**, albeit with much lower stereoselectivity (entry 3). Cyclization of malonate derivative **7** was complete within minutes at rt (entry 4), indicating a strong, positive Thorpe−Ingold effect to the reaction rate and efficiency. The reaction of amide **8** required several hours for completion and showed that the method is also applicable to the synthesis of heterocycles (entry 5). Entries 6 and 7 show that the reaction allows for the cyclohexane ring-closure. When considering moderate yields in these last two examples, one should keep in mind that an unsubstituted open chain is the most difficult substrate for cyclization and that any substitution would enhance the propensity of the substrate for the ring-closure. However, the reaction appears to be restricted to the formation of five- and six-membered rings, as attempts to perform 3-exo- or 7-exo-cyclizations under similar conditions failed.

With this new cyclization method in hand, we revisited our synthetic problem. Gratifyingly, the cyclization of **11** was complete within minutes at rt, affording the desired product **16** in 95% yield (entry 8)![15] Oxidation of this intermediate with oxone gave the corresponding ester **1**;[16] thus, the overall cyclization/oxidation sequence was a successful synthetic equivalent of the unfeasible ester enolate cyclization.

The next logical step was to examine whether the cyclization could be performed as a catalytic asymmetric reaction. Initial screening of organocatalysts was not successful, as they either did not catalyze the reaction (MacMillan's catalyst, (*S*)-proline, (*S*)-2-diphenylprolinol) or failed to effect the asymmetric induction ((*S*)-2-methoxymethyl pyrrolidine). Better results were obtained when the role of the asymmetric inductor was conferred to the metal complex. Thus, reaction of **7** with 3 mol % of Pd[(*R*)-(+)-(BINAP)] catalyst at 0 °C afforded the product with 36% ee, albeit in lower yield. However, lowering the temperature to −20 °C gave, after 4 h, the product **13** with 91% ee (Scheme 3, example 1).

Scheme 3. Catalytic Asymmetric Cyclizations



Similarly, optically enriched pyrrolidine derivative **14** was obtained with 59% ee, when the reaction was performed at 0 °C (example 2). However, in this case the reaction required

(15) Preparation of **16**: Pyrrolidine (123.6 mg, 145 μL, 1.74 mmol) was added to a solution of tetrakis(triphenylphosphine)palladium (183 mg, 0.174 mmol) and aldehyde **11** (542 mg, 1.15 mmol) in THF (250 mL), with stirring, under an argon atmosphere. After 1.5 h the solvent was removed under reduced pressure, and the concentrate was taken up in dichloromethane (150 mL). The solution was washed with 2% aq HCl, water, aq $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by dry-flash chromatography (SiO_2, eluent 3% ethyl acetate in petroleum ether) afforded 458 mg (96%) of the title compound **16**, as a colorless oil. Physical data for **16**: IR_{film}: 2933, 2862, 1725, 1255, 1073, 1040, 837, 777, 700. ^1H NMR (δ): 9.50 (d, J = 3.0 Hz, 1H), 7.27−7.36 (m, 5H), 5.86−6.04 (m, 1H), 5.05−5.14 (m, 2H), 4.54 (s, 2H), 3.67 (dd, J^1 = 2.2 Hz, J^2 = 3.7 Hz, 1H), 3.41 (dd, J^1 = 1.8 Hz, J^2 = 3.7 Hz, 1H), 2.65−2.72 (m, 1H), 1.90−2.05 (m, 1H), 1.36−1.45 (m, 2H), 0.90 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H). ^{13}C NMR (δ): 205.3, 180.1, 138.4, 128.3, 127.7, 127.5, 117.1, 116.7, 81.8, 73.0, 70.8, 48.6, 42.4, 41.0, 29.6, 26.8, 25.7, 18.1. $[\alpha]_D$ +42 (*c* 1 EtOAc). Anal. calcd for $C_{23}H_{36}O_3Si$: C 71.08, H 9.34; found: C 71.08, H 9.49.

(16) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

8 days for completion, and for practical reasons, it was not possible to run the cyclization at a lower temperature.

To summarize, a new cyclization reaction is developed, based on double catalysis—a synergic combination of organocatalysis and transition-metal catalysis—which allows for the efficient synthesis of 5- and 6-membered rings. The cyclization is stereoselective and can also be performed as a catalytic asymmetric reaction. Research directed toward establishing the scope and limitations of the reaction, and the search for the optimal ligands and organocatalysts, is underway.

Acknowledgment. This research was supported by the Serbian Ministry of Science and environmental protection. R.N.S. is grateful to Professor Pierre Potier (deceased on February 3, 2006) for the invitation to perform a part of this research at the I.C.S.N., and also gratefully acknowledges the hospitality of Professor Jean-Yves Lallemand and Dr. Jean Boivin, as well as stimulating discussions with Professor Sam Z. Zard, Dr. Mikhail Ermolenko, Dr. Emmanuel Roulland, and Dr. Branislav Musicki.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7023554