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# Surprisingly Mild "Enolate-Counterion-Free" Pd(0)-Catalyzed Intramolecular Allylic Alkylations

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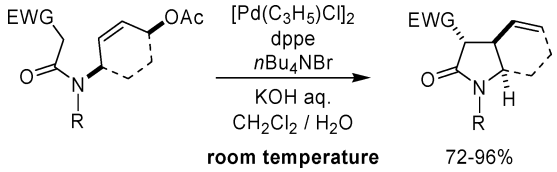
## ABSTRACT

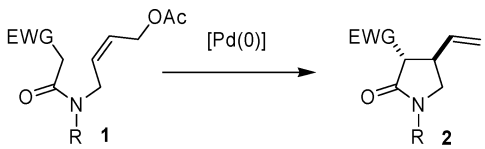



**Palladium-catalyzed intramolecular allylic alkylations of unsaturated EWG-activated amides can take place under phase-transfer conditions or in the presence of a crown ether. These new reaction conditions are milder and higher yielding than those previously reported. A rationalization for such an unexpected result is put forth and validated by DFT-B3LYP calculations. The results suggest cyclization via a counterion-free (*E*)-enolate TS.**

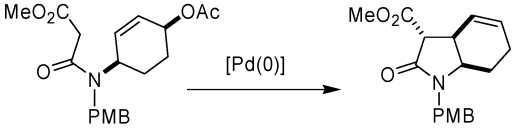
Following our ongoing interest in the synthesis of nitrogen-based heterocycles, we recently reported that $\gamma$-lactams could be regio- and stereoselectively built up via the intramolecular 5-*exo* interaction between a stabilized acetamide enolate anion and a properly tethered $\eta^3$-allyl-palladium appendage (Scheme 1).[1]

Although we found that these cyclizations could be efficiently promoted by different palladium-based catalytic systems such as BSA[2]/AcOK/$PPh_3$/THF or NaH/$Pd(OAc)_2$/dppe/DMF (Table 1, entries 1 and 2)[3] or in the presence of $Ti(O^iPr)_4/CH_2Cl_2$ as an enolizing agent (entry 3),[4] heating or even reflux of the solvent was constantly necessary to bring these reactions to completion. Thus, for example, when the conditions of entry 2 were repeated at room temperature,

**Scheme 1**




**a**: EWG= $CO_2Me$; R= Bn. **b**: EWG= $CO_2Me$; R=PMB
**c**: EWG=CN, R=Bn. **d**: EWG=COMe; R=Bn
**e**: EWG=SPh; R=Bn. **f:** EWG=$SO_2Ph$; R=Bn




**3** **4**

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(1) (a) Giambastiani, G.; Pacini, B.; Porcelloni, M.; Poli, G. *J. Org. Chem.* **1998**, *63*, 804−807. (b) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456−9459. (c) Thorimbert, S.; Giambastiani, G.; Commandeur, C.; Vitale, M.; Poli, G.; Malacria, M. *Eur. J. Org. Chem.* **2003**, 2702−2708. (d) Lemaire, S.; Giambastiani, G.; Prestat, G.; Poli, G. *Eur. J. Org. Chem.* **2004**, 2840−2847.

(2) BSA: *N*,*O*-Bis(trimethylsilyl)acetamide.

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**Table 1.** Palladium-Catalyzed Cyclization of Unsaturated Acetamides **1** to **2**

| entry | precatalyst (5 mol %) | precursor | ligand (12.5 mol %) | base (equiv) | additive (equiv) | solvent | temp (°C) | time (h) | product | yield (%)[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | $Pd_2(dba)_3$ | **1a** | $PPh_3$ [b] | BSA/AcOK[c] | | THF | reflux | 12 | **2a** | 69 |
| 2[3] | $Pd(OAc)_2$ | **1a** | dppe | NaH (1.1) | | DMF | 90 | 2 | **2a** | 75 |
| 3[4] | $Pd_2(dba)_3$ | **1a** | $PPh_3$ [b] | $Ti(O^iPr)_4$ (1.2) | | $CH_2Cl_2$ | reflux | 12 | **2a** | 75 |
| 4 | $Pd(OAc)_2$ | **1a** | dppe | NaH (1.1) | | DMF | rt | 24 | **2a** | 0 |
| 5 | $[Pd(C_3H_5)Cl]_2$ | **1a** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 2 | **2a** | 90 |
| 6 | $[Pd(C_3H_5)Cl]_2$ | **1a** | dppe | aq KOH (2.0) | $n$-$Bu_4NHSO_4$ (0.1) | $CH_2Cl_2$ | rt | 2 | **2a** | 93 |
| 7 | $Pd(OAc)_2$ | **1b** | dppe | NaH (1.1) | | DMF | 90 | 2 | **2b** | 65 |
| 8 | $[Pd(C_3H_5)Cl]_2$ | **1b** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 2 | **2b** | 95 |
| 9 | $[Pd(C_3H_5)Cl]_2$ | **1c** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 2 | **2c**[d] | 96 |
| 10 | $[Pd(C_3H_5)Cl]_2$ | **1d** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 0.5 | **2d** | 82 |
| 11 | $[Pd(C_3H_5)Cl]_2$ | **1e** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 72 | **2e**[e] | 72 |
| 12 | $[Pd(C_3H_5)Cl]_2$ | **1f** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 0.5 | **2f** | 94 |
| 13 | $Pd(OAc)_2$ | **3** | dppe | NaH (1.1) | | DMF | 90 | 2 | **4** | 80 |
| 14 | $[Pd(C_3H_5)Cl]_2$ | **3** | dppe | aq KOH (2.0) | $n$-$Bu_4NBr$ (0.1) | $CH_2Cl_2$ | rt | 2 | **4** | 82 |
| 15 | $Pd(OAc)_2$ | **1a** | dppe | NaH (1.1) | 15-C-5 (1.2) | DMF | rt | 2 | **2a** | 76 |
| 16 | $Pd(OAc)_2$ | **1a** | dppe | NaH (1.1) | 15-C-5 (0.2) | DMF | rt | 2 | **2a** | 54 |
| 17 | $Pd(OAc)_2$ | **1a** | dppe | NaH (0.1) | 15-C-5 (0.2) | DMF | rt | 24 | **2a** | 68 |

[a] Isolated yields. A single diastereoisomer was observed unless otherwise stated. [b] Performed with 50 mol % $PPh_3$. [c] BSA 1.2 equiv; AcOK 10 mol %. [d] Product was obtained as a 75/25 diastereomeric mixture. [e] Product was obtained as a 93/7 diastereomeric mixture.

total recovery of the starting material was observed (compare entries 2 and 4). The manifest difficulty of such an apparently favored 5-*exo* cyclization was especially puzzling in light of the ease of most Pd(0)-catalyzed allylic alkylation processes, which are normally carried out at room temperature even in entropically less favored intermolecular processes.[5] In the hope of finding milder reaction conditions, and possibly of understanding the reasons of such a seemingly low reactivity, we thus decided to pursue alternative reaction conditions in our cyclization studies. In particular, we decided to direct our investigations toward phase-transfer catalysis (PTC),[6] known to be compatible with palladium chemistry.[7]

After a few preliminary assays, we found that the use of $n$-$Bu_4NBr$ (10 mol %) as the phase-transfer agent, $[Pd(C_3H_5)Cl]_2$ (5 mol %) as the palladium source, dppe (12.5 mol %) as the ligand, and KOH (2.0 equiv) as the base, in a biphasic $CH_2Cl_2/H_2O$ (1/1; v/v) system, resulted in substantial improvement. Indeed, under these conditions the unsaturated amide **1a** smoothly afforded the desired cyclization product **2a** (90% yield) *at room temperature and without traces of ester saponification* (entry 5). Interestingly, the same result was obtained by replacing $n$-$Bu_4NBr$ with $n$-$Bu_4NHSO_3$. It thus appears that the bromide anion has no major role in this reactivity enhancement (entry 6).[8] Furthermore, the beneficial effect of the new reaction conditions could be cleanly reproduced on the more synthetically interesting *N*-PMB-protected substrate **1b** (compare entries 7 and 8).

Interestingly, the nature of the acetamide-activating group could also be switched with unchanged success, as shown in the cyclization of the cyano-, acetyl-, phenylsufenyl-, and phenylsulfonyl-activated precursors **1c**−**f**, respectively (entries 9−12).

The smooth conversion of the cyclic precursor **3** into the hexahydroindolone **4** is of particular mechanistic relevance. In fact, the involvement of a $\eta^3$-allyl complex incorporated into a cyclic structure automatically rules out $\eta^3$-allyl *anti*−*syn* isomerization as the possible reason for substrate activation (compare entries 13 and 14). Thus, these new conditions appear to be far more efficient than those previously used.

Cyclizations in the presence of a suitable Na-sequestering agent, such as a crown ether, were next tested. To our satisfaction, the cyclization of the model compound **1a** under the same NaH/DMF/$Pd(OAc)_2$/dppe-based reaction conditions as those originally used, except for the presence of the 15-C-5 (1.2 equiv), took place at *room temperature* to give the expected product in 76% yield (Table 1, entry 15). More conveniently, the same protocol could be performed in the presence of a substoichiometric amount of crown ether with only marginal yield erosion (entry 16). Finally, cyclization

(3) Lemaire, S.; Prestat, G.; Giambastiani, G.; Madec, D.; Pacini, B.; Poli, G. *J. Organomet. Chem.* **2003**, *687*, 291−300.

(4) Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* **1999**, *64*, 2962−2965.

(5) For reviews, see: (a) Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons: New York, 2002; pp 1669−1844. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(6) For generalities on phase-transfer catalysis, see: (a) Demlow, E. V.; Demlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993. (b) Goldberg, Y. *Phase Transfer Catalysis: Selected Problems and Applications*; Gordon & Breach Science Publishers: Reading, PA, 1992. (c) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994.

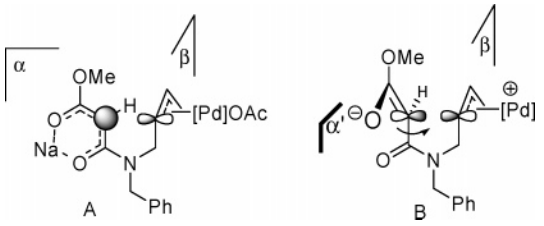
(7) (a) Poli, G.; Madec, D. *Chemtracts: Org. Chem.* **2002**, *15*, 498−505. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418−7423 (c) Nakoji, M.; Kanayama, T.; Okino, Y.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (d) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567.

(8) For a review on the effect of halides in transition metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47.

of **1a** at room temperature could be achieved again using catalytic amounts of both NaH (0.1 equiv) and 15-C-5 (0.2 equiv) as long as the reaction time was increased (entry 17).

As far as the mechanistic rationalization of the results is concerned, we reasoned that the remarkable efficacy of these new reaction conditions could be directly related to the particular nature of the enolate counterion. Indeed, upon NaH deprotonation, the malonamide substrates are expected to give rise to planar, resonance-stabilized, Na-chelated enolates, which are at the same time conjugated with the intrinsically planar amide function. As a consequence, in the ground-state conformation of the reactive intermediate, all twelve[9] atoms making up the Na-chelated malonamide enolate will roughly lie in the same α plane (Scheme 2, A).

**Scheme 2**




On the other hand, in an ideal intermolecular enolate/$\eta^3$-allyl−PdX interaction, optimal orbital overlap requires a parallel disposition between the plane containing the enolate (α′) and that containing the allyl fragment ($\beta$). We can thus infer that the transition state (TS) of the cyclization process (Scheme 2, B) has to feature a significant loss of conjugation with respect to the Na-chelated ground-state conformation.

As a consequence, we believe that the remarkable reactivity of these new cyclization conditions is likely to be due to the generation of a highly reactive zwitterionic[10] enolate/$\eta^3$-allyl intermediate, that can be achieved under either biphasic PTC conditions or Na-sequestered homogeneous conditions (Scheme 3).[11]

To support the above speculation, and in line with our earlier contribution in this area,[12] we have performed a computational model study. Accordingly, we have used a small model system for the Pd−allyl enolate intermediate, $(H_3P)_2Pd[CH_2CHCH]-CH_2-NMe-CO-CHCHO$, and located the different possible metal-free TSs at the B3LYP/LACVP* level of theory in Jaguar v 4.2.[13] The solvent was simulated as a continuum using the PB-SCRF model[14] in Jaguar with parameters appropriate for dichloromethane.[15] The relative energies for the eight possible TSs are shown in Table 2.

**Scheme 3.** Chelated vs Counterion-Free Pathway in the Cyclization of **1** to **2**

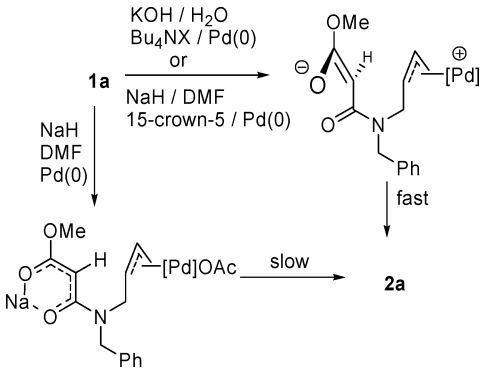



**Table 2.** Relative Energies and Length of the Forming Bond for the Eight Possible TSs

| entry | *syn*/*anti* allyl | *endo*/*exo* | *E*/*Z* | $E_{rel}$ (kJ/mol) | C−C bond length (Å) |
|---|---|---|---|---|---|
| 1 | *syn* | *exo* | *E* | 0.0 | 2.62 |
| 2 | *syn* | *exo* | *Z* | 12.5 | 2.69 |
| 3 | *syn* | *endo* | *E* | 81.9 | 2.79 |
| 4 | *syn* | *endo* | *Z* | 100.0 | 2.78 |
| 5 | *anti* | *exo* | *E* | 5.1 | 2.63 |
| 6 | *anti* | *exo* | *Z* | 20.9 | 2.71 |
| 7 | *anti* | *endo* | *E* | 53.6 | 2.58 |
| 8 | *anti* | *endo* | *Z* | 65.9 | 2.60 |

One immediately notices the large energy difference between *endo* and *exo* cyclization. In all cases, the *exo* cyclization is favored by more than 30 kJ/mol compared to the most facile of the *endo* cyclization pathways. In Figure 1 are shown the two most accessible TSs, corresponding to entries 1 and 5 in Table 2.

Compared to our earlier model calculations, which included the $Na^+$ counterion, the transitions states are earlier and more reactant-like. The forming bond has a length of over 2.6 Å in the TS, as compared to ca. 2.4 Å when the $Na^+$ counterion was included (Figure 1).

This indicates that the free anion is inherently more reactive than the chelated complex, as expected. Looking more closely at the geometries of the TSs, we see that

(9) Methyl groups in methyl esters are known to favor a planar *s-cis* conformation. See for example: *Stereoelectronic Effects in Organic Chemistry*; Deslongchamps, P., Ed.; Pergamon Press: Oxford, 1983.

(10) At present we cannot rule out the alternative ionization by anionic palladate species $[L_2Pd(OAc)]Na$, which would result in a completely naked enolate instead of the zwitterionic form, in line with the observations of Amatore, Jutand, and co-workers: Amatore, C.; Jutand, A.; M'Barki, M. A.; Meyer, G.; Mottier, L. *Eur. J. Inorg. Chem.* **2001**, 873−880. However, the reaction does not seem to be sensitive to the presence of halides; cf. entries 5 and 6, Table 1.

(11) Deprotonation of the pronucleophile under biphasic PTC conditions is expected to take place in the interfacial region. (a) Makosza, M.; Krylowa, I. *Tetrahedron* **1999**, *55*, 6395−6402. (b) Mason, D. Magdassi, S.; Sasson, Y. *J. Org. Chem.* **1990**, *55*, 2714−2717. (c) Gobbi, A.; Landini, D.; Maia, A.; Petricci, S. *J. Org. Chem.* **1998**, *63*, 5356−5361. (d) Lygo, B.; Andrews, B. *Acc. Chem. Res.* **2004**, *37*, 518−525.

(12) Norrby, P.-O.; Mader, M. M.; Vitale, M.; Prestat, G.; Poli, G. *Organometallics* **2003**, *22*, 1849−1855.

(13) *Jaguar 4.2*; Schrödinger, Inc.: Portland, OR, 2000. See: http://www.schrodinger.com.

(14) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, *100*, 11775−11788.

(15) Solvent model is essential for the success of the calculations; without it, the ring closure occurs without a barrier: Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem. Eur. J.* **1999**, *5*, 902−909.

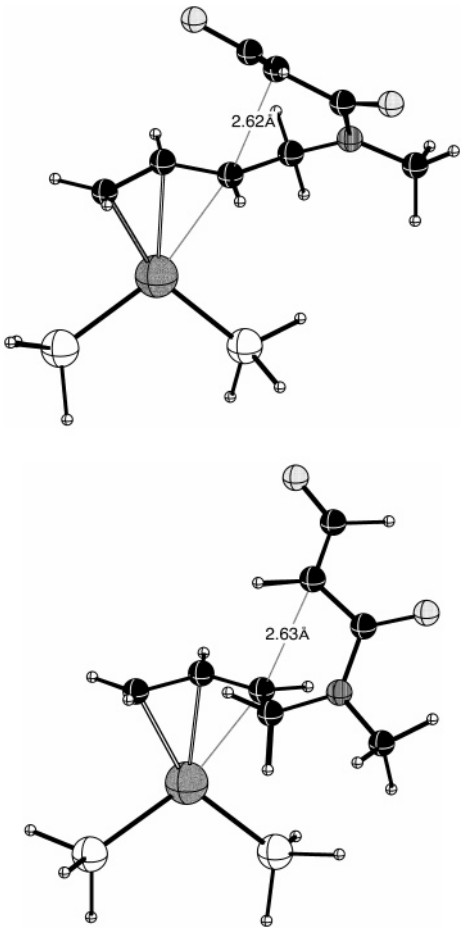



**Figure 1.** Two energetically most favorable TSs. Top: *syn*, *exo*, *E* (Table 2, entry 1), below: *anti*, *exo*, *E* (Table 2, entry 5).

exclusion of the counterion also allows the nucleophile to deviate from planarity. In our previous study, we showed that there is substantial strain induced in the planar amide in the TS; in the absence of $Na^+$, this strain can be somewhat relieved by a rotation (ca. 20−25°) of the planar enolate with respect to the amide, leading to a more facile ring closure. Finally, we noted that in the absence of the chelating counterion, which enforces a (*Z*)-configuration on the enolate, the free form can also exist as the (*E*)-isomer. It was found that, in all cases, the (*E*)-form has a lower barrier to ring closure, by 13−18 kJ/mol, corresponding to a rate increase of 2−3 orders of magnitude. In all, the combination of these three effects fully rationalizes the observed rate increase upon exclusion of chelating counterions. Finally, it should be noted that the geometrical effects observed here also may have bearing on other cases where strong counterion effects have been observed.[16]

In summary, we have shown a new and operationally very simple protocol for the Pd-catalyzed intramolecular alkylation of unsaturated EWG-activated amides that relies on the in situ generation of a highly reactive metal counterion-free enolate/$\eta^3$-allyl complex. The new reaction conditions allow the cyclization of the tested precursors to take place in better yields and with milder reaction conditions than originally reported. A rationale accounting for such a marked reactivity enhancement is provided. Extension to asymmetric variants of the present method is currently under investigation.

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**Supporting Information Available:** General procedures, spectroscopic data for all new compounds, Cartesian coordinates, and energies of all calculated complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) See for example: Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123,* 3671−3686.