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Platinum-catalyzed Desaturation of Lactams, Ketones and Lactones

Ming Chen[†], Alexander J. Rago[†] and Guangbin Dong*[,†]

In memory of Professor Jack Halpern.

Abstract: The development of a general platinum-catalyzed desaturation of *N*-protected lactams, ketones, and lactones to their conjugated α,β-unsaturated counterparts is reported. The reaction is operated under mildly acidic conditions at room temperature or 50 °C. It is scalable and tolerates a wide range of functional groups. The complementary reactivity to the palladium-catalyzed desaturation is demonstrated in the efficient conversion of iodide, bromide and sulfur-containing substrates.

Desaturation of carbonyl compounds is a strategically important transformation.[1] This is not only because the resulting electron-deficient conjugated alkenes are frequently found in bioactive natural products and drugs (Figure 1),[2] but also because these α,β-unsaturated moieties are often utilized as versatile intermediates for subsequent β-functionalization or α,β-difunctionalization of carbonyl compounds.[3] Among various α,β-desaturation methods, the catalytic approaches are primarily dominated by using palladium, which involves formation of a Pd(II)-enolate, followed by β-hydrogen elimination and further oxidation of the Pd(0) intermediate back to the Pd(II) catalyst.[4] While it has been demonstrated to be a highly powerful reaction for desaturating a diverse range of carbonyl compounds, including ketones, esters, cyanides, carboxylic acids and amides efficiently,[5] some limitation still exists for the palladium catalysis. For example, Pd(0) is known to undergo facile oxidative addition with aryl iodides and halogen-abstraction with alkyl halides,[6] thus compatibility of these structural motifs in the Pd-catalyzed desaturation could be a major concern (*vide infra*, Table 3). Scattered examples of using other transition metals, such as Cu,[7] Ir[8] and Ru[9], for catalytic desaturation of carbonyl compounds have also been reported, but the generality of these methods has not been fully established. Stimulated by such a chemoselectivity challenge, we herein describe the development of a *platinum*-catalyzed desaturation method suitable for various lactams, ketones, and lactones with complementary reactivity to the palladium catalysis.

Despite in the same group, homogeneous platinum catalysis has found much fewer applications compared with palladium catalysis to date.[10] We were inspired by the facts that oxidative addition of Pt(0) with C−X (X: halogen) bonds is less common than the one of Pd(0)[11] and β-hydrogen elimination with a Pt(II) enolate has been observed by Hartwig and co-workers[12] (Scheme 1a). Thus, we hypothesized that Pt(II) salts could be capable of catalyzing ketone desaturation without affecting these redox-active C−X bonds (Scheme 1b).

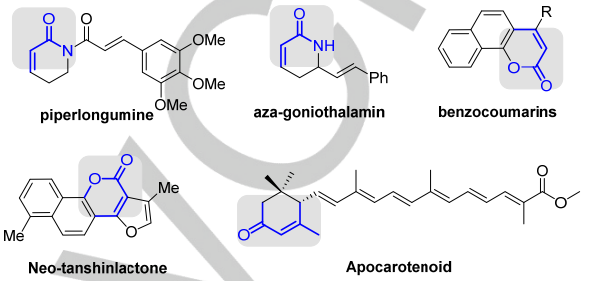
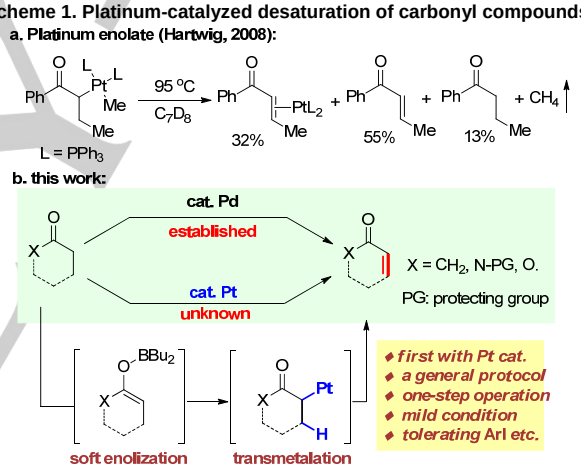


Figure 1. Representative bioactive natural products and drugs containing α,β-unsaturated carbonyl moieties.

Scheme 1. Platinum-catalyzed desaturation of carbonyl compounds



To test the hypothesis, valeroalactam **1a** was employed as a model substrate. Indeed, when using $Pt(COD)Cl_2$ as the pre-catalyst, a catalytic amount of AgTFA as a chloride scavenger, and diallyl carbonate (DAC) as the oxidant, the desired α,β-unsaturated lactam **2a** was obtained in 98% yield at room temperature through *in situ* forming a boron-enolate intermediate (Table 1).[5m,13] To gain more insights of this reaction, the role of each reactant was explored through control experiments. First, no product was observed without $Pt(COD)Cl_2$ or AgTFA (entries 1 and 2). A range of other metal complexes has also been examined (entry 3). First, $PtCl_2$ cannot catalyze this reaction and $Pt(MeCN)_2Cl_2$ only gave a 15% yield. In contrast, using $Pt(COD)(TFA)_2$ in the absence of the silver salt still afforded 80% yield of **2a**, which indicated that the TFA anion is important and the silver metal is not critical for the reactivity. Other metal complexes except Pd gave no or low reactivity. While $Pd(TFA)_2$ could still give 41% yield of the desired product **2a**, its efficiency is lower than the $Pt(COD)Cl_2$/AgTFA system; interestingly, the corresponding $Pd(COD)Cl_2$/AgTFA combination gave no desired product. A number of oxidants have been examined (entry 4). The quinone-type oxidants previously used in the Pd-catalyzed

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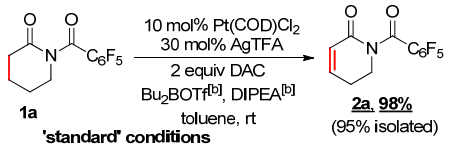
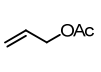
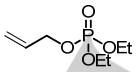
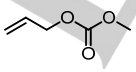
desaturation[5m] showed low to moderate reactivity, whereas the allyl oxidants employed by Newhouse and co-workers[5g,5h] were found to be more effective in this case. Ultimately, allyl carbonates proved to be superior. Unsurprisingly, soft enolization using Bu_2BOTf and DIPEA remained critical for the lactam activation (entries 5 and 6). The platinum loading could be further reduced to 5-6 mol% without significantly compromising the yield (entries 7 and 8). A survey of solvent effect suggested that aromatic solvents, such as toluene and fluorobenzene, are optimal, although 1,4-dioxane also delivered the product in 92% yield (entries 9 and 10).

Table 1. Selected optimization studies.



Entry	Variations from the 'standard' conditions	Yield (%) of **2a**[a]
1	Without **Pt(COD)Cl$_2$**	0
2	Without **AgTFA**	0
3	**C2-7** instead of **Pt(COD)Cl$_2$**	Listed below
4	**Ox2-7** instead of **Ox1**	Listed below
5	Without **Bu$_2$BOTf**	0
6	Without **DIPEA**	6
7	6 mol% **Pt(COD)Cl$_2$**	96[d]
8	5 mol% **Pt(COD)Cl$_2$**	88[d]
9	solvent = PhF	98
10	solvent = 1,4-dioxane	92
11	solvent = THF	11
12	solvent = MeCN or DCM	0

PtCl$_2$ **C2,** 0%	**Pt(MeCN)$_2$Cl$_2$** **C2,** 15%	**Pt(COD)(TFA)$_2$** **C4,** 80%[c]
Pd(COD)Cl$_2$ **C5,** 0%	**[Rh(COD)Cl]$_2$** **C6,** 0%	**Ru(COD)Cl$_2$** **C7,** 0%
(DME)NiCl$_2$ **C8,** 0%	**[Ir(COD)Cl]$_2$** **C9,** 6%	**Pd(TFA)$_2$** **C10,** 41%[c] (96%)[d]
BQ **Ox2**, 16%	2,5-di-*t*Bu-BQ **Ox3**, 10%	tetra-Me-BQ **Ox4**, 44%
 **Ox5**, 68%	 **Ox6**, 10%	 **Ox7**, 94%

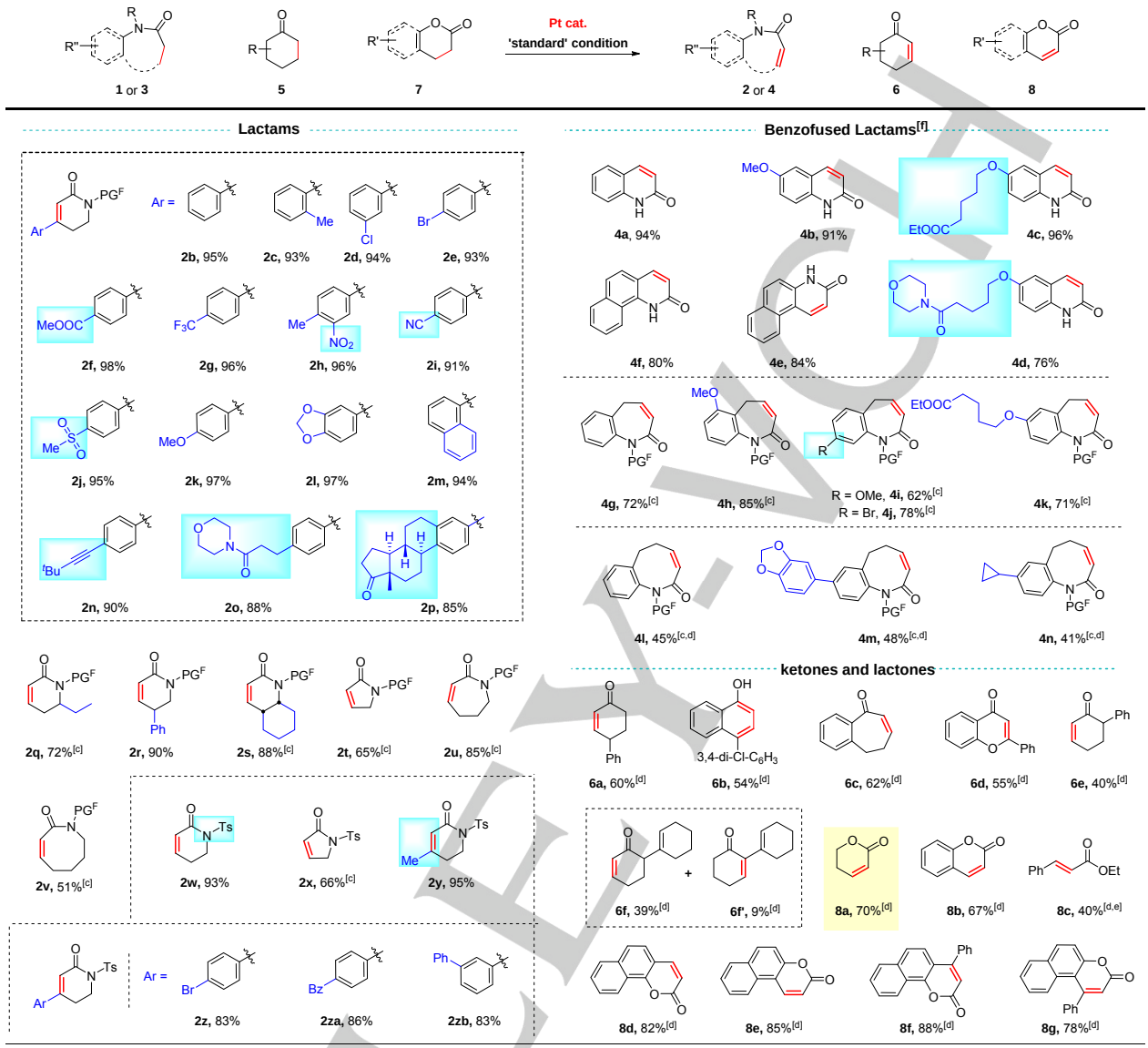
[a] Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial for 24 h; yields were determined by ^{1}H NMR using CH_2Br_2 as the internal standard. [b] 1.3 equiv. [c] No AgTFA was added. [d] 50 °C was used. TFA = trifluoroacetate, DAC = diallyl carbonate, COD = 1,5-cyclooctadiene.

With the optimized conditions in hand, the substrate scope was explored (Table 2). First, various substitutions on valeroalactams at the β, γ, and δ-positions can all be tolerated (**2a-2s**). Note that, compared with the prior Pd system,[5m] higher yields and full conversion for these lactams were obtained with the Pt catalyst. This is advantageous because it is typically very difficult to separate the unsaturated products from the remaining starting materials; for example, pure products **2m**, **2n**, and **2p** were not obtained previously under the Pd-catalyzed conditions.[5m] Gratifyingly, a wide range of functional groups were compatible, which included aryl chloride (**2d**), bromide (**2e**), ester (**2f**), trifluoromethyl (**2g**), nitro (**2h**), nitrile (**2i**), sulfone (**2j**), ketone (**2p**), electron-rich aromatic rings (**2k** and **2l**) and alkyne (**2n**). In the presence of an additional enolizable tertiary amide, desaturation of lactam **1o** still occurred selectively at the lactam moiety. In addition, lactams with different ring sizes (**2t**-**2v**) were effective substrates. Moreover, Ts was not a suitable protecting group in the prior Pd-catalyzed desaturation; but here good to excellent yields of the Ts-protected lactams were achieved,[14] suggesting that the platinum condition is more general.

Next, benzofused lactams with different ring sizes were examined. In the case of benzofused six-member ring substrates, high yields and excellent chemoselectivity were observed and the products underwent simultaneous deprotection to give 2-quinolones **4a-4f**. Benzofused seven- and eight-membered substrates also worked; fluorobenzene was found to be a better solvent for the benzofused eight-membered compounds (**4l-4n**). Finally, the feasibility of desaturating ketones and lactones was also tested with the Pt catalysis (**6a-8g**). Cyclohexanones and benzofused six- and seven-membered ketones were competent substrates. Note that desaturation of 2-substituted cyclohexanones preferred to occur at the less sterically hindered side. δ-Lactones with or without benzofused scaffolds could give the corresponding unsaturated products. A linear ester (**8c**) also reacted albeit in a lower efficiency.

To show the complementarity of this method to the Pd-catalyzed desaturation, substrates containing aryl iodides, alkyl bromides and thioethers were investigated under both the Pt and Pd catalysis conditions (Table 3). It is clear that aryl iodides (**9a**, **9c**, **9e**, **9f**, **9g** and **9j**) that were not tolerated under the Pd conditions did not interfere with the reactions catalyzed by platinum. On the other hand, substrates that contain alkyl bromides (**9b**, **9d** and **9h**)[15] gave low yields with the Pd catalysis; but they worked well under the Pt conditions. Recently, we found that thioethers could direct sp^3 C−H activation reaction using Pd catalysis;[16] while such a substrate (**9i**) gave no desired product with Pd, it became a competent substrate for the Pt-catalyzed desaturation. Thus, the platinum-catalyzed desaturation can be more chemoselective.

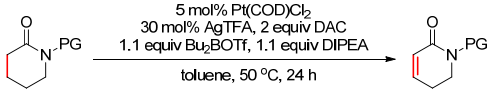
Table 2. Substrate scope with lactams, ketones and lactones.[a,b]



[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 24 h. [b] Isolated yields. [c] 50 °C was used. [d] PhF was used as the solvent. [e] Separation of the pure product from the starting material was difficult and 24% of the starting material remained. [f] These products underwent simultaneous deprotection during the desaturation reaction. $PG^F = COC_6F_5$. Ts= *p*-toluenesulfonyl.

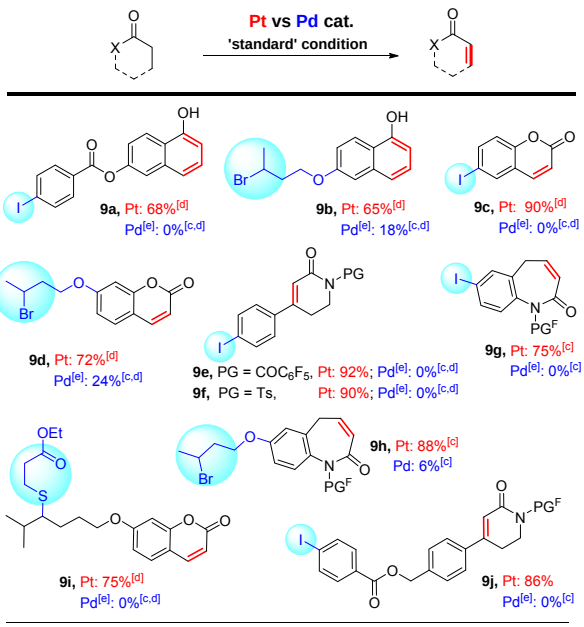
To test the practicality of this method, gram-scale reactions were carried out with 5 mol% of the platinum pre-catalyst. Satisfactory yields were obtained with either the perfluorobenzoyl- or Ts-protected substrates (Scheme 2). A variety of transformations has been employed to extend the utilities of this desaturation method (Scheme 3). First, the acyl protecting group could be easily removed to reveal the free lactam (**10**) under mild conditions. The α,β-unsaturated lactams could undergo diverse efficient conjugate addition reactions to form β-tertiary or quaternary stereocenters through C−C, C−N, C−S and C-Si bond formation.[18]

Scheme 2. Gram-scale reactions.



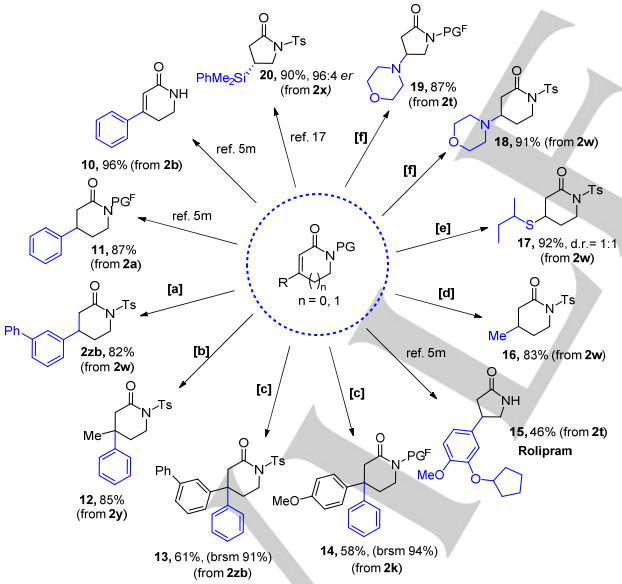
2a, PG = PG^F, 80%, 1.16 g
2w, PG = Ts, 88%, 1.1 g

Table 3. Complementary to the Pd-catalyzed desaturation.[a,b]



[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 24 h. [b] Isolated yields. [c] 50 °C was used. [d] PhF as solvent. [e] Pd condition: 10 mol% $Pd(TFA)_2$ was used instead of $Pt(COD)Cl_2$ and no AgTFA was added (see Table 1, **C10**).

Scheme 3. Synthetic utilities.



[a] 1.5 equiv 1,1'-biphenyl-3-ylboronic acid, 2.5 mol% $[Rh(COD)Cl]_2$, 2 M K_3PO_4 in dioxane, rt, 12 h; [b] 2 equiv $PhB(OH)_2$, 5 mol% $Pd(TFA)_2$, 6 mol% bipyridine in 50 mM NaTFA, 100 °C, 6 h; [c] 4 equiv $PhB(OH)_2$, 5 mol% $Pd(TFA)_2$, 6 mol% bipyridine in 50 mM NaTFA, 100 °C, 6 h; [d] 2.1 equiv MeMgBr, 1.2 equiv CuBr•MS, 3 equiv TMSCl in THF, 2 h; [e] 1.1 equiv butane-2-thiol and 5 mol% NaH in DCM, 50 °C, 12 h; [f] 2 equiv morpholine in toluene, 50 °C, 12 h; brsm: based on recovered starting material.

In summary, the first platinum-catalyzed desaturation of carbonyl compounds has been developed. The reaction operates at room temperature or 50 °C, with tolerating a wide range of functional groups. Complementary features to the prior palladium-catalyzed methods have been disclosed. Such a unique chemoselectivity could be useful for complex molecule synthesis. It is also anticipated that the unique mode of reactivity discovered here should inspire the future exploration of other platinum-catalyzed reactions.

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Keywords: desaturation • lactam • ketone • lactone • platinum catalysis

[1] a) D. R. Buckle, I. L. Pinto, *In Comprehensive Organic Synthesis*, (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, *7*, 119; b) K. C. Nicolaou, N. A. Petasis, *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, **1984**; Chapter 3; c) J. Muzart, *Eur. J. Org. Chem*. **2010**, 3779.

[2] a) R. C. Barcelos, J. C. Pastre, D. B. Vendramini-Costa, V. Caixeta, G. B. Longato, P. A. Monteiro, J. E. Carvalho, R. A. Pilli, *ChemMedChem* **2014**, *9*, 2725; b) V. R. Rao, P. Muthenna, G. Shankaraiah, C. Akileshwari, K. H. Babu, G. Suresh, K.S. Babu, R. S. C. Kumar, K. R. Prasad, P. A. Yadav, J. M. Petrash, G. B. Reddy, J. M. Rao, *Eur. J. Med. Chem*. **2012**, *57*, 344; c) Y. Dong, Q. Shi, Y-N. Liu, X. Wang, K. F. Bastow, K-H. Lee, *J. Med. Chem.* **2009**, *52*, 3586; d) X. Wang, K. F. Bastow, C-M. Sun, Y-L. Lin, H-J. Yu, M-J. Don, T-S. Wu, S. Nakamura, K-H. Lee, *J. Med. Chem.* **2004**, *47*, 5816; e) M. D. Méndez-Robles, H. H. Permady, M. E. Jaramillo-Flores, E. C. Lugo-Cervantes, A. Cardador-Martinez, A. A. Canales-Aguirre, F. Lopez-Dellamary, C. M. Cerda-Garcia-Martinez, A. A. Canales-Aguirre, F. Lopez-Dellamary, C. M. Cerda-Garcia-Rojas, J. Tamariz, *J. Nat. Prod*. **2006**, *69*, 1140.

[3] a) B. E. Rossiter, N. M. Swingle, *Chem. Rev*. **1992**, *92*, 771; b) A. Gutnov, *Eur. J. Org. Chem*. **2008**, 4547; c) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; d) Z. Huang, G. Dong; *Tetrahedron Lett*. **2014**, *55*, 5869; e) M. J. Chapdelaine, M. Hulce in *Organic Reactions*, Vol. 38, (Eds.: L. A. Paquette), Wiley, New York, **1990**, 225; f) Y. Chen, D. Huang, Y. Zhao, T. R. Newhouse, *Angew. Chem. Int. Ed*. **2017**, *56*, 8258.

[4] a) S. S. Stahl, T. Diao, *Comp. Org. Synth.* **2014**, *7*, 178; b) D. Wang, A. B. Weinstein, P. B. White,S. S. Stahl, *Chem. Rev.* **2018**, *118*, 2636; c) A. Turlik, Y. Chen, T. R. Newhouse, *Synlett* **2016**, 331.

[5] For leading references, see: a) R. J., Theissen, *J. Org. Chem.***1971**, *36*, 752. b) Y. Ito, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011; c) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209; d) D. Pun, T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8213; e) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566; f) T. Diao, D. Pun, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8205; g) Y. Chen, J. P. Romaire, T. R. Newhouse, *J. Am. Chem. Soc.* **2015**, *137*, 5875; h) Y. Chen, A. Turlik, T. R. Newhouse, *J. Am. Chem. Soc.* **2016**, *138*, 1166; i) A. Turlik, Y. Chen, T. R. Newhouse, *Synlett* **2016**, *27*, 331; j) Y. Zhao, Y. Chen, T. R. Newhouse, *Angew. Chem. Int. Ed.* **2017**, *56*, 13122; k) D. Huang, Y. Zhao, T. R. Newhouse, *Org. Lett.* **2018**, *20*, 684; l) S. M. Szewczyk, Y. Zhao, H. A. Sakai, P. Dube, T. R. Newhouse, *Tetrahedron* **2018**, *74*, 3293; m) M. Chen, G. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 7757.

[6] J. Tsuji in *Palladium Reagents and Catalysts, New Perspectives for the 21th Century,* Wiley, Chichester, **2004**.
[7] a) X. Jie, Y. Shang, X. Zhang, W. Su, *J. Am. Chem. Soc*. **2016**, *138*, 5623; b) Y. Shang, X. Jie, K. Jonnad, S. N. Zafar, W. Su, *Nat. Commun*. **2017**, *8*, 2273; c) L. Liang, G. Yang, F. Xu, Y. Niu, Q. Sun, P. Xu, *Eur. J. Org. Chem*. **2013**, 6130.
[8] a) Z. Wang, Z. He, L. Zhang, Y. Huang, *J. Am. Chem. Soc.* **2018**, *140*, 735; b) M. G. Manas, L. S. Sharninghausen, E. Lin, R. H. Crabtree, *J. Organomet. Chem.* **2015**, *792*, 184.
[9] a) C. S. Yi, D. W. Lee, *Organometallics* **2009**, *28*, 947.
[10] a) J. A. Labinger, *Chem. Rev*. **2017**, *117*, 8483; b) F. Dénès, A. Pérez-Luna, F. Chemla, *Chem. Rev*. **2010**, *110*, 2366; c) G. K. Anderson, *Platinum-Carbon σ-Bonded Complexes. In Comprehensive Organometallic Chemistry* II, (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Elsevier: Oxford, U.K., **1995**, 9, 431; d) *Chemistry of the Platinum Group Metals* (Hrsg.: F. R. Hartley), Elsevier, Amsterdam, **1991**.
[11] C. Mateo, C. Fernández-Rivas, D. J. Cárdenas, A. M. Echavarren, *Organometallics* **1998**, *17*, 3661.
[12] E. J. Alexanian, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 15627.
[13] Y. Sakamoto, T. Amaya, T. Suzuki, T. Hirao, *Chem. Eur. J*. **2016**, *22*, 18686.
[14] Boc and regular benzoyl were found still not suitable protecting groups.
[15] C. Wang, G. Dong, *J. Am. Chem. Soc.* **2018**, *140*, 6057.
[16] L. Jin, J. Wang, G. Dong, *Angew. Chem. Int. Ed.* **2018**, 57, 12352.
[17] V. Pace, J. P. Rae, D. J. Procter, *Org. Lett.* **2014**, *16*, 476.
[18] a) R. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1992**; b) T. Senda, M. Ogasawara, T. Hayashi, *J. Org. Chem*. **2001**, 66, 6852; c) M. Pineschi, F. D. Moro, F. Gini, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 1244; d) R. V. Zeeland, L. M. Stanley, *ACS Catal.* **2015**, *5*, 5203; e) G. R. Dake, M. D. B. Fenster, P. B. Hurley, B. O. Patrick, *J. Org. Chem*. **2004**, *69*, 5668

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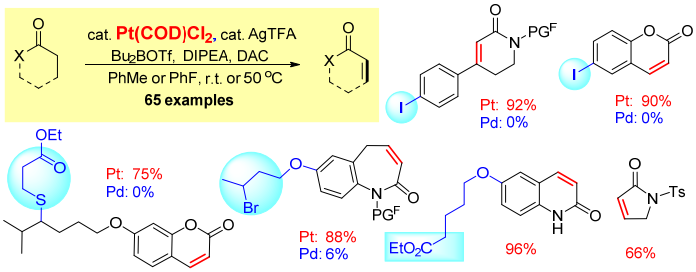
Platinum-catalyzed Desaturation of Lactams, Ketones and Lactones



The first platinum-catalyzed desaturation of *N*-protected lactams, ketones and lactones is reported. The reaction is operated under mild conditions, scalable and chemoselective. In particular, functional groups incompatible under the palladium-catalyzed desaturation conditions were tolerated by the platinum catalyst.