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Alpha-Oxo-Ketenimines from Isocyanides and Alpha-Haloketones: Synthesis and Divergent Reactivity

Mathias Mamboury, Qian Wang, and Jieping Zhu*

Abstract: *The palladium-catalyzed reaction of α-haloketones with isocyanides afforded α-oxo-ketenimines through β-hydride elimination of the β-oxo-imidoyl palladium intermediates. Reaction of these relatively stable α-oxo-ketenimines with nucleophiles such as hydrazines, hydrazoic acid, amines, and Grignard reagent afforded pyrazoles, tetrazole, β-keto amidines and enaminone, respectively, with high chemoselectivity. While amines attack exclusively on the ketenimine functions, the formal [3+2] cycloaddition between N-monosubstituted hydrazines and α-oxo-ketenimines was initiated by nucleophilic addition to the carbonyl group.*

The isoxazolium salt (Woodward's reagent K) has been used as an activating reagent of carboxylic acids and phosphoric acids for peptide synthesis[1] and for phosphorylation,[2] respectively. The true activating species has been identified to be the α-oxo-ketenimine generated *in situ* and indeed a stable *N-tert*-butylketoketenimine was isolated from the reaction of *N-tert*-butyl-5-phenylisoxazolium perchlorate with trimethylamine.[3] Since this seminal contribution, two principal methods have been developed for the synthesis of α-oxo-ketenimines **1**: a) the Wittig reaction of phosphoranes **2** with isocyanates **3**;[4] b) the Aza-Wittig reaction of α-oxo-ketenes **4** with aza-phosphoranes **5**.[5] While these two transformations work well in most of the cases, they do need elaborated and not-so-stable starting materials and are not atom-economic.[6]

The carbene like reactivity of isocyanide has made it one of the most versatile reactants in the design of novel multicomponent reactions.[7] The availability of the lone-pair electron of the divalent carbon also rendered it an excellent σ-donating ligand. This last property, while well exploited in organometallic chemistry,[8] has hampered to certain extent its use in transition metal catalyzed transformations. However, the last 15 years have witnessed the significant progress in palladium-catalyzed isocyanide insertion reactions involving C(sp^2)-Pd[9-11] and more recently C(sp^3)-Pd species.[12] We have recently reported a palladium-catalyzed reaction of isocyanides with allyl carbonates for the synthesis of ketenimines. Migratory insertion of isocyanide to (η^1-allyl)-Pd complex followed by β–hydride elimination of the resulting allylimidoylpalladium intermediate[13] was proposed to account for the formation of ketenimines.[14] Independently, the group of Yang,[15] Wu and Jiang[16] have developed similar approaches starting from 2-bromophosphonates and propargylic carbonates, respectively.

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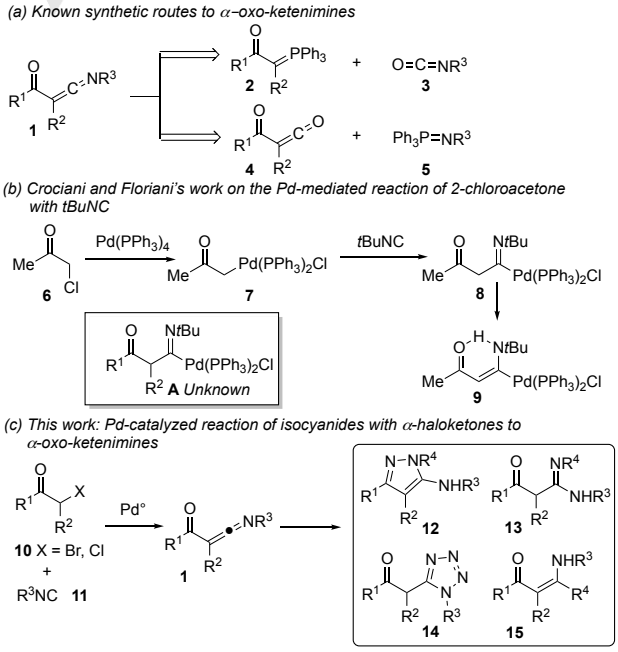
As a continuation of this research program, we became interested in the reaction of α-haloketones with isocyanides. In 1984, Crociani and co-workers reported that reaction of 2-chloroacetone (**6**) with $Pd(PPh_3)_4$ afforded carbon σ-bonded palladium complex **7** which, upon addition of *tert*-butylisocyanide. was converted to enaminone complex **9** via the imidoylpalladium intermediate **8**.[17] Floriani confirmed the reaction sequence by X-ray crystal structural analysis of the palladium complexes **7** and **9**.[18] Due probably to the need of using stoichiometric amount of Pd, this interesting transformation remained dormant without being exploited in synthetic organic chemistry. We reasoned that by using secondary α-acyl alkylhalides, the hypothetic intermediate **A** ($R^2 \neq H$) might undergo reaction different from that defined for **8**. Instead of tautomerization to enamine that would introduce significant allylic strains, a β–hydride elimination from **A** would occur preferentially to afford α-oxo-ketenimines with concurrent regeneration of Pd species and therefore making the entire process catalytic. We report the successful realization of this endeavor as well as the exploration of the divergent chemical reactivity of this highly functionalized species **1** for the synthesis of 5-aminopyrazoles **12**, β-keto amidines **13**, tetrazoles **14** and enaminones **15**, important heterocycles and building blocks in organic synthesis (Scheme 1).

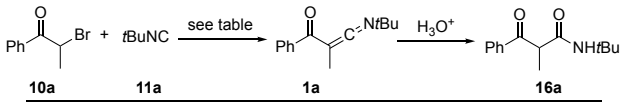


Scheme 1. Synthesis of α-oxo-ketenimines.

Under conditions we previously optimized for the synthesis of ketenimines,[14a] the reaction between 2-bromo-1-phenyl propan-1-one (**10a**) and *tert*-butylisonitrile (**11a**) afforded indeed the desired α-oxo-ketenimine **1a**, albeit in moderate yield (entry 1, Table 1). After systematic screening of the base (entries 1-3), the solvent (entries 1, 4-5), the palladium source (entries 5-7) and the temperature (entries 5, 8-9), the optimum conditions

found consisted of performing the reaction in toluene (*c* 0.2) in the presence of $Pd(OAc)_2$ (0.05 equiv), K_2CO_3 (2.0 equiv) at 60 °C. Under these conditions, **1a** was formed in 81% isolated yield (entry 8). Reducing the loading of palladium acetate and the amount of potassium carbonate afforded product in diminished yields (entries 10,11). We note that the reaction outcome was very sensitive to the reaction temperature (entries 5, 9 vs 8) and that the reaction was inhibited under air atmosphere (entry 12). The α-oxo-ketenimine **1a** can be *in situ* hydrolyzed (10% aq. HCl) to deliver β-keto amide **16a** in 79% isolated yield. Of note, 2-chloropropiophenone reacted equally well with **11a** to afford, after hydrolysis, **16a** in 75% yield. Remarkably, phenyl vinyl ketone resulting from the β-H elimination of the $C(sp^3)$-PdBr complex (*Vide Supra,* Scheme 5, intermediate **B**) was not detected in the reaction mixture.

Table 1. Optimization of the formation of α-oxo-ketenimine **1a**.

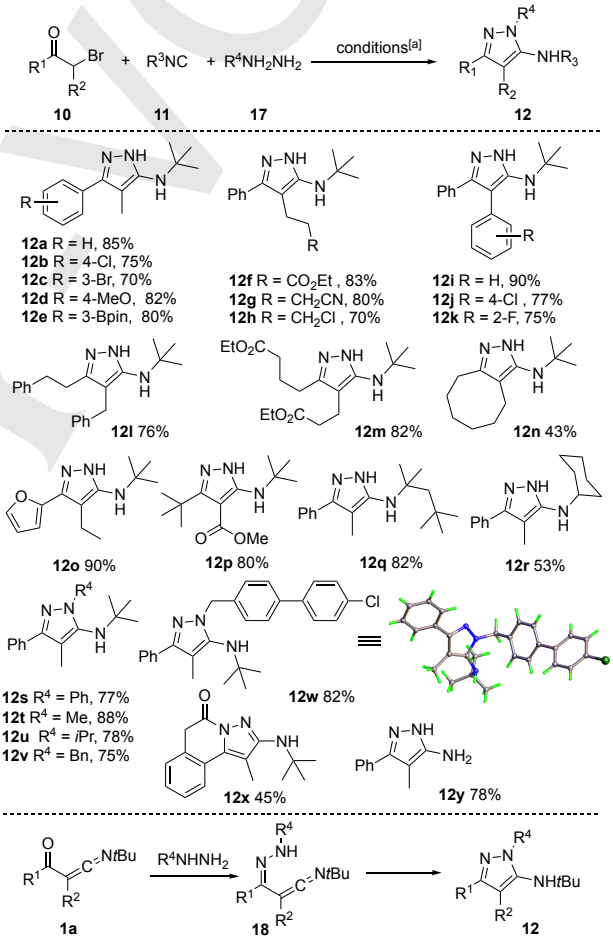


10a **11a** **1a** **16a**

Entry	Palladium	Base	Solvent	Temp.	**1a** [a,b]
1	$Pd(OAc)_2$	K_2CO_3	THF	50 °C	34%
2	$Pd(OAc)_2$	Cs_2CO_3	THF	50 °C	13%
3	$Pd(OAc)_2$	K_3PO_4	THF	50 °C	34%
4	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	50 °C	53%
5	$Pd(OAc)_2$	K_2CO_3	toluene	50 °C	71%
6	$Pd(TFA)_2$	K_2CO_3	toluene	50 °C	51%
7	$PdCl_2$	K_2CO_3	toluene	50 °C	49%
8	**$Pd(OAc)_2$**	**K_2CO_3**	**toluene**	**60 °C**	**84%(81%)**
9	$Pd(OAc)_2$	K_2CO_3	toluene	70 °C	18%
10	$Pd(OAc)_2$	K_2CO_3	toluene	60 °C	58%[c]
11	$Pd(OAc)_2$	K_2CO_3	toluene	60 °C	77%[d]
12	$Pd(OAc)_2$	K_2CO_3	toluene	60 °C	trace[e]

[a] Standard conditions: **10a** (0.4 mmol), *t*BuNC (0.48 mmol), palladium (0.05 equiv), base (0.8 mmol), solvent (2.0 mL), argon; [b] NMR yield using CH_2Br_2 as standard, yield in parenthesis corresponds to pure isolated product; [c] $Pd(OAc)_2$ (0.025 equiv); [d] K_2CO_3 (0.48 mmol); [e] under air.

The 5-aminopyrazole is an important class of heterocycles in pharmaceutical and agrochemical industries.[19] Particularly, *N*-aryl-5-aminopyrazoles have been recognized as a privileged motif in medicinal chemistry.[20] With an efficient synthesis of α-oxo-ketenimines in hand, a one-pot three-component synthesis of 5-aminopyrazoles was next sought. Gratefully, stirring a toluene solution of **10a** and **11a** under our optimized conditions [$Pd(OAc)_2$ (0.05 equiv), K_2CO_3 (2.0 equiv), 60 °C] followed by addition of a THF solution of hydrazine (**17a**, 2.0 equiv) at room temperature afforded 5-aminopyrazole **12a** in 85% isolated yield (Scheme 2). This three-component reaction was applicable to a wide range of substrates. Both electron-withdrawing (**12b**-**12c**) and electron-donating (**12d**) groups on the aromatic moiety of 2-bromopropiophenone were tolerated. Notably, aryl bromide (**12c**) and aryl boronate (**12e**) were compatible to this palladium-catalyzed transformation. Electrophilic functionalities such as ester (**12f**), cyanide (**12g**) and even alkyl chloride (**12h**), which are susceptible to nucleophilic attack by hydrazine, remained untouched to deliver the desired products in high yields. 3,4-Diaryl substituted 5-aminopyrazoles could be formed (**12i-12k**), as well as 3,4-dialkyl derivatives (**12l-12n**). A furan unit was also compatible leading to **12o** in 90% isolated yield. α-Bromo-β-ketoester participated in the reaction affording **12p** in 80% yield. Isocyanides other than *t*BuNC including, most importantly, a secondary isocyanide, reacted successfully (**12q-12r**). The reaction with *N*-aryl or *N*-alkyl substituted hydrazines was found to be highly regioselective leading to the tetrasubstituted 5-aminopyrazoles (**12s-12w**) in excellent yields. The structure of **12w** was confirmed by X-ray crystallographic analysis.[21] Reaction of methyl 2-[2-(2-bromoacetyl)phenyl]acetate with *tert*-butylisonitrile and hydrazine afforded tricyclic compound **12x** in 45% isolated yield. Finally, cleavage of the *tert*-butyl group of **12a** [$BF_3{\cdot}Et_2O$ (10 equiv), dichloroethane, 50 °C] afforded **12y** in 78% yield. Such unsubstituted 5-aminopyrazoles are useful building blocks in the synthesis of more complex heterocyclic scaffolds.[22]

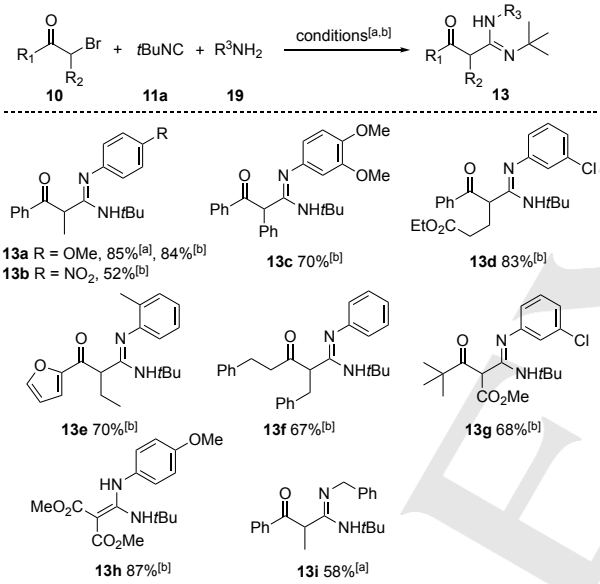


Scheme 2. Scope of the one-pot three-component synthesis of 5-aminopyrazoles from α-bromoketones. [a] Standard conditions: α-bromoketone (0.4 mmol), isocyanide (0.48 mmol), $Pd(OAc)_2$ (0.05 equiv), K_2CO_3 (0.8 mmol), toluene (2.0 mL), argon, 60 °C; then NH_2NH_2 (0.8 mmol), room temperature. [b] when hydrochloride salts $R^4NHNH_2{\cdot}HCl$ were used, KOH (1.0 equiv) was added to the reaction mixture.

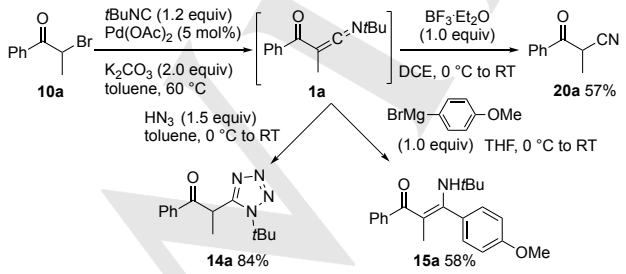
The exclusive formation of regioisomer **12s-12w** could be accounted for by chemoselective addition of hydrazine to carbonyl rather than the ketenimine function leading to intermediate **18** which, upon cyclization, would afford the observed products **12s-12w**. This observed chemoselectivity is intriguing based on the known reactivity pattern of α-oxo-ketenimine (see below). We note that there was one single example in the literature dealing with the reaction of

phenylhydrazine with α-oxo-ketenimine and a regioisomeric pyrazole was assigned to the adduct.[5]

Interestingly, the addition occurred chemoselectively on the ketenimine rather than on the carbonyl function when amine was used as a nucleophile. Thus, the reaction of the crude α-oxo-ketenimine **1a** with *p*-anisidine (1.0 equiv) at 90 °C afforded β-keto amidine **13a** in 85% yield (conditions a). In the presence of a catalytic amount of TFA (0.2 equiv, RT), the reaction proceeded with the same chemoselectivity to afford **13a** in a similar yield but with shorter reaction time (condition b). The generality of this protocol is shown in Scheme 3. Various α-bromo aryl alkyl ketone, aryl aryl ketone, alkyl alkyl ketone, β-keto ester and malonate participated in this reaction. Both electron-rich (**13a**, **13c**, **13h**), electron-poor (**13b**, **13d**, **13g**) and hindered (**13e**) anilines were efficient nucleophilic partners, so was aliphatic amine (**13i**). It is worth noting that there were very few methods allowing the direct access to β-keto amidines. A sulfide contraction reaction is a notable example in this regard.[23]



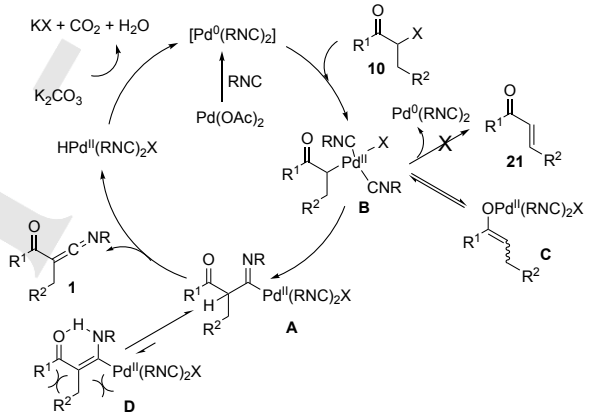
Scheme 3. Scope of the three-component synthesis of β-keto amidines from α-bromoketones. Standard conditions: α-bromoketone (0.4 mmol), *t*BuNC (0.48 mmol), $Pd(OAc)_2$ (0.05 equiv), K_2CO_3 (0.8 mmol), toluene (2.0 mL), argon, 60 °C; then [a] amine (0.4 mmol), toluene (2.0 mL), 90 °C; [b] amine (0.4 mmol), TFA (0.2 equiv), toluene (2.0 mL), room temperature.



Scheme 4. Further structural diversification of α-oxo-ketenimine **1a**.

Further examples of the synthetic transformation of the α-oxo-ketenimine are depicted in Scheme 4. Treatment of the crude ketenimine **1a** with boron trifluoride etherate afforded α-cyanoketone **20a** in 57% yield. Reaction of **1a** with HN_3 in toluene delivered tetrazole **14a** in 84% yield. Finally, treatment of **1a** with Grignard reagent provided enaminone **15a** in 58% yield resulting from the chemoselective nucleophilic addition to the ketenimine function. We note that classic synthesis involving the condensation of *tert*-butylamine with the corresponding 1,3-diketone would not afford **15a** with such a high regioselectivity.

A plausible reaction pathway accounting for the formation of α-oxo-ketenimines **1** is described in Scheme 5. Oxidative addition of α-haloketone **10** to the *in situ* generated Pd^0 species[24] would afford intermediate **B** which might be in equilibrium with *O*-bound tautomer **C**.[25] Migratory insertion of RNC from **B** would generate imidoylpalladium intermediate **A** which could tautomerize to **D** according to Crociani and Floriani[17-18]. However, we assumed that the presence of the CH_2R^2 group would impose severe steric interaction in the tetrasubstituted enaminone form **D**. Therefore, the equilibrium may not take place or reside mainly on the imine form **A**. The β-hydride elimination[13-14] from **A** would deliver the desired α-oxo-ketenimine **1** with concurrent regeneration of Pd catalyst.



Scheme 5. Mechanistic hypothesis.

The palladium-catalyzed carbonylation of α-haloketones is known and till now the scope of this synthetically useful transformation was applied mainly to haloketones lacking the β-hydrogen[26] since intermediate related to **B** are known to undergo rapid β-hydride elimination to enone **21** even under the carefully optimized conditions.[27] The fact that this supposedly facile process, a main concern at the outset of our reaction design, did not take place under our conditions is remarkable. The migratory insertion might be sufficiently fast from isocyanide-ligated Pd species **B** to outcompete the β-hydride elimination process.

In summary, we reported a new protocol for the preparation of α-oxo-ketenimines from α-haloketones and isocyanides taking advantage of a palladium-catalyzed isocyanide insertion/β-hydride elimination sequence. A one-pot three-component synthesis of tri- and tetrasubstituted 5-aminopyrazoles was subsequently developed by trapping *in situ* the α-oxo-ketenimines with hydrazines. When amines/anilines, azide and Grignard reagent were used as nucleophiles, nucleophilic addition occurred chemoselectively on the ketenimine function to

afford the β-keto amidines, tetrazole and enaminone, respectively.

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Keywords: palladium • isocyanide • ketenimine • heterocycle • amidine

[1] a) R. B. Woodward, R. A. Olofson, H. Mayer, *J. Am. Chem. Soc.* **1961**, *83*, 1010; b) R. B. Woodward, R. A. Olofson, *J. Am. Chem. Soc.* **1961**, *83*, 1007; c) D. J. Woodman, A. I. Davidson, *J. Org. Chem.* **1973**, *38*, 4288.

[2] F. Cramer, H. Neunhoeffer, K. H. Scheit, G. Schneider, J. Tennigkeit, *Angew. Chem.* **1962**, *74*, 387; *Angew. Chem. Int. Ed.* **1962**, *1*, 331.

[3] R. B. Woodward, D. J. Woodman, *J. Am. Chem. Soc.* **1966**, *88*, 3169.

[4] a) X. Zhou, J. Zheng, L. Xue, P. Lu, Y. Wang, *Eur. J. Org. Chem.* **2015**, 5789; b) X. Zhou, Z. Fan, Z. Zhang, P. Lu, Y. Wang, *Org. Lett.* **2016**, *18*, 4706.

[5] L. Capuano, K. Djokar, N. Schneider, C. Wamprecht, *Liebigs Ann. Chem.* **1987**, 183.

[6] Other methods, see: a) G. Buono, *Tetrahedron Lett.* **1973**, 5167; b) J. Ichikawa, N. Yokota, M. Kobayashi, K. Amano, T. Minami, *Synlett* **1996**, 243.

[7] J. Zhu, Q. Wang, M.-X. Wang, *Multicomponent Reaction in Organic Synthesis*, **2015**, Wiley-VCH: Weinheim.

[8] R. A. Michelin, A. J. L. Pombeiro, A. F. Guedes da Silva, *Coord. Chem. Rev*. **2001**, *218*, 75.

[9] For pioneering contributions, see: a) C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem.* **2000**, *112*, 4326; *Angew. Chem. Int. Ed*. **2000**, *39*, 4156; b) K. K. R. Tetala, R. J. Whitby, M. E. Light, M. H. Hurtshouse, *Tetrahedron Lett.* **2004**, *45*, 6991; c) C. G. Saluste, S. Crumpler, M. Furber, R. J. Whitby, *Tetrahedron Lett*. **2004**, *45*, 6995; d) M. Kosugi, T. Ogata, H. Tamura, H. Sano, T. Migita, *Chem. Lett*. **1986**, 1197; e) T. Ishiyama, T. Oh-e, A. Suzuki, *Tetrahedron Lett*. **1992**, *33*, 4465.

[10] For recent selected examples, see: a) G. C. Senadi, W.-P. Hu, S. S. K. Boominathan, J.-J. Wang, *Chem. Eur. J.* **2015**, *21*, 998; b) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai, J.-Q. Yu, *Nature* **2014**, *515*, 389; c) P. Mampuys, Y. Zhu, T. Vlaar, E. Ruijter, R. V. A. Orru, B. U. W. Maes, *Angew. Chem.* **2014**, *126*, 13063; *Angew. Chem. Int. Ed.* **2014**, *53***,** 12849; d) N. Thirupathi, M. H. Babu, V. Dwivedi, R. Kant, M. S. Reddy, *Org. Lett*. **2014**, *16*, 2908; e) T. Tang, X.-D. Fei, Z.-Y. Ge, Z. Chen, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem.* **2013**, *78*, 3170; f) J. Liu, Z. Liu, N. Wu, P. Liao, X. Bi, *Chem. Eur. J.* **2014**, *20*, 2154; g) V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Lang, *J. Org. Chem.* **2013**, *78*, 1471; h) F. Ji, M.-f. Lv, W.-b. Yi, C. Cai, *Adv. Synth. Catal*. **2013**, *355*, 3401; i) K. Nanjo, S. Yamamoto, C. Tsukano, Y. Takemoto, *Org. Lett*. **2013**, *15*, 3754; j) C.-H. Lei, D.-X. Wang, L. Zhao, J. Zhu, M.-X. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 4708; k) G. Qiu, C. Chen, L. Yao, J. Wu, *Adv. Synth. Catal*. **2013**, *355*, 1579; l) J. V. Geden, A. K. Pancholi, M. Shipman, *J. Org. Chem*. **2013**, *78*, 4158; m) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem.* **2012**, *124***,** 13235; *Angew. Chem. Int. Ed.* **2012**, *51***,** 13058; n) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett*. **2012**, *14*, 4270; o) Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett*. **2011**, *13*, 4604; p) H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org. Lett*. **2011**, *13*, 1028; q) T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi, M. Murakami, *Org. Lett*. **2011**, *13*, 1429; r) M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835; s) For a mechanistic study, see: L. A. Perego, P. Fleurat-Lessard, L. El Kaim, I. Ciofini, L. Grimaud, *Chem. Eur. J.* **2016**, *22*, 15491.

[11] For recent reviews on metal-catalyzed insertion reactions, see: a) A. V. Lygin, A. de Meijere, *Angew. Chem.* **2010**, *122*, 9280; *Angew. Chem. Int. Ed*. **2010**, *49*, 9094; b) M. Tobisu, N. Chatani, *Chem. Lett.* **2011**, *40*, 330; c) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257; d) S. Lang, *Chem. Soc. Rev.* **2013**, *42*, 4867; e) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem.* **2013**, *125*, 7222; *Angew. Chem. Int. Ed.* **2013**, *52***,** 7084; f) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal*. **2014**, *356*, 2135; g) B. Song, B. Xu, *Chem. Soc. Rev*. **2017**, *46*, 1103; h) M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron, J. Zhu, *Chem. Soc. Rev*. **2017**, *46*, 1295.

[12] a) H. Jiang, H. Gao, B. Liu, W. Wu, *Chem. Commun.* **2014**, *50*, 15348; b) J. Wang, S. Luo, J. Huang, T. Mao, Q. Zhu, *Chem. Eur. J.* **2014**, *20*, 11220; c) W. Kong, Q. Wang, J. Zhu, *Angew. Chem.* **2016**, *128*, 9866; *Angew. Chem. Int. Ed*. **2016**, *55*, 9714.

[13] For the first report of β-hydride elimination leading to ketenimine, see: Y. Ito, T. Hirao, N. Ohta, T. Saegusa, *Tetrahedron Letters* **1977**, *18*, 1009.

[14] a) G. Qiu, M. Mamboury, Q. Wang, J. Zhu, *Angew. Chem.* **2016**, *128*, 15603; *Angew. Chem. Int. Ed.* **2016**, *55*, 15377; b) G. Qiu, Q. Wang, J. Zhu, *Org. Lett.* **2017**, *19*, 270.

[15] Q. Yang, C. Li, M.-X. Cheng, S.-D. Yang, *ACS Catal.* **2016**, *6*, 4715.

[16] a) J. Peng, Y. Gao, W. Hu, Y. Gao, M. Hu, W. Wu, Y. Ren, H. Jiang, *Org. Lett.* **2016**, *18*, 5924–5927.

[17] R. Bertani, C. B. Castellani, B. Crociani, *J. Organomet. Chem*. **1984**, *269*, C15.

[18] P. Veya, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1993**, *12*, 4899.

[19] For a recent review, see: R. Aggarwal, V. Kumar, R. Kumar, S. P. Singh, *Beilstein J. Org. Chem.* **2011**, *7*, 179.

[20] M. Marinozzi, G. Marcelli, A. Carotti, *Mini. Rev. Med. Chem.* **2015**, *15*, 272.

[21] CCDC 1554575 (**12w**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

[22] Synthesis of aminopyrazoles from α-halogenketone hydrazones and isocyanides, see: V. Atlan, C. Buron, L. El Kaim, *Synlett* **2000**, 489,

[23] W. Heffe, R. W. Balsiger, K. Thoma, *Helv. Chim. Acta*. **1974**, *57*, 1242.

[24] a) Y. Ito, M. Suginome, T. Matsuura, M. Murakami, *J. Am. Chem. Soc.* **1991**, *113*, 8899; b) L. A. Perego, P. Fleurat-Lessard, L. El Kaïm, I. Ciofini, L. Grimaud, *Chem. Eur. J.* **2016**, *22*, 15491.

[25] a) H. Urata, H. Suzuki, Y. Moro-Oka, T. Ikawa, *J. Organomet. Chem.* **1982**, *234*, 367; b) A. C. Albéniz, N. M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571; c) D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816.

[26] a) J. K. Stille, P. K. Wong, *J. Org. Chem.* **1975**, *40*, 532; b) 2-chlorocyclohexanone has been successfully employed, see: S. Perrone, M. Capua, A. Salomome, L. Troisi, *J. Org. Chem.* **2015**, *80*, 8189.

[27] B. Wahl, H. Bonin, A. Mortreux, S. Giboulot, F. Liron, G. Poli, M. Sauthier, *Adv. Synth. Catal.* **2012**, *354*, 3105.

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Synthetic Method

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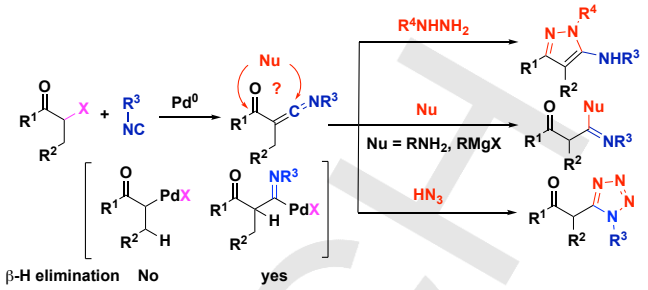
Alpha-Oxo-ketenimines from Isocyanides and Alpha-Haloketones: Synthesis and Divergent Reactivity



β-Hydride elimination at will. Reaction of *α-haloketones with isocyanides in th presence of a catalytic amount of Pd(OAc)₂ afforded α-oxo-ketenimines that can b further converted to 5-aminopyrazoles, tetrazole, β-keto amidines and enaminone i good to excellent yields.*