Synthesis of Pyrrolidines and Pyrrolizidines with α-Pseudoquaternary Centers by Copper-Catalyzed Condensation of α-Diazodicarbonyl Compounds and Aryl γ-Lactams

Goudedranche, Sébastien; Besnard, Céline; Egger, Leo; Lacour, Jérôme

How to cite

GOUDEDRANCHE, Sébastien et al. Synthesis of Pyrrolidines and Pyrrolizidines with α-Pseudoquaternary Centers by Copper-Catalyzed Condensation of α-Diazodicarbonyl Compounds and Aryl γ-Lactams. In: Angewandte Chemie, 2016, vol. 55, n° 44, p. 13775–13779. doi: 10.1002/anie.201607574

This publication URL: https://archive-ouverte.unige.ch/unige:88396

Publication DOI: 10.1002/anie.201607574

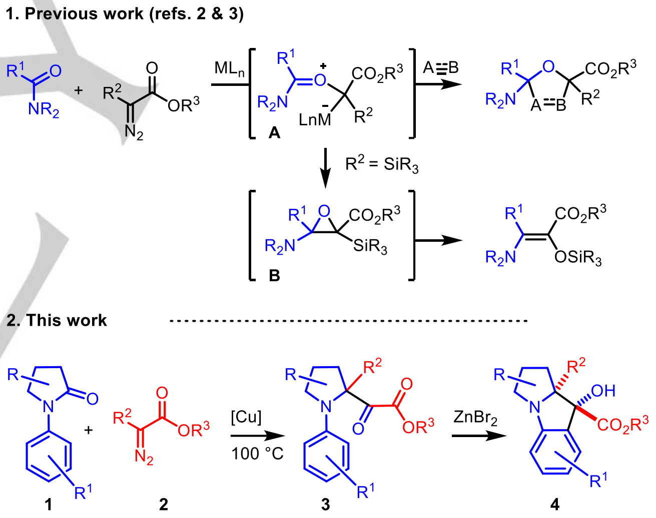
Synthesis of pyrrolidines and pyrrolizidines with α-pseudoquaternary centers by Cu-catalyzed condensation of α-diazodicarbonyls and aryl γ-lactams

Sébastien Goudedranche, Céline Besnard, Léo Egger and Jérôme Lacour*

Abstract: Under copper-catalysis exclusively, *N*-aryl γ-lactams react intermolecularly with acceptor-acceptor diazo reagents, usually dicarbonyls, to yield functionalized pyrrolidines carrying α-pseudoquaternary centers. Thanks to preferred [1,2]-migrations of acyl or phosphoryl groups, single regioisomers are obtained. Furthermore, in the presence of a *Lewis* acid, subsequent Friedel-Crafts reactions occur yielding tricyclic pyrrolizidines in excellent yields (90-96%) and diastereoselectivity (up to and higher than 20:1).

Tertiary amides and lactams are known to react with diazo ester reagents and form carbonyl ylide intermediates **A** in the presence of catalytic amounts of metal salts or complexes (Scheme 1, top).[1] As a rule, these [1,3]-dipoles undergo [3+2]-cycloadditions with alkenes and alkynes yielding elaborate polycyclic frameworks when the reactions are performed intramolecularly.[2] Of interest for the current study, when silyl substituents are present on the diazo reagent, epoxide intermediates **B** are formed resulting, after silyl group migration, into amino silyl enol ethers.[3],[4] Herein, in a new development, the intermolecular reactivity of *N*-aryl γ-lactams **1** with α-diazo dicarbonyls **2** is reported (Scheme 1, bottom).[5] Highly functionalized pyrrolidines **3** carrying α-pseudoquaternary centers are obtained (yields up to 83%).[6] In fact, in one step, the amide group is transformed into an amine with two adjacent acetyl and 2-oxoethanoate chains. The transformation, which involves acyl (or phosphoryl) group migrations, proceeds with very high regioselectivity and uses copper salts as catalysts specifically (10 mol%). In the presence of *Lewis* acids, intramolecular Friedel-Crafts reactions can further occur (**3**→**4**) yielding tricyclic pyrrolizidines in excellent yields (90-96%) and selectivity (diastereomeric ratio, *d.r.* ≥ 18:1). In view of their valuable heterocyclic structures,[7] products **3** and **4** should be of interest in a variety of fields, *eg*, in peptide or medical chemistry; their preparation being difficult to imagine by another route.

Recently, metal-catalyzed decompositions of acceptor-acceptor α-diazo dicarbonyl reagents have been studied in our group to afford, in the presence of *Lewis* bases, an extended range of reactivity.[8] For instance, under CpRu catalysis and using aldehydes, ketones, lactones and cyclic carbonates as substrates, dioxolene ketals, orthoesters and orthocarbonates were obtained.[9] In view of this reactivity involving carbonyl ylide intermediates, reactions of diazo dicarbonyl reagents with amides and lactams were attempted. For this study, *N*-aryl pyrrolidinones were selected as substrates. In a first experiment, 1-phenyl-2-pyrrolidinone **1a** was treated with methyl diazoacetoacetate **2A** in dichloromethane (DCM) in the presence of [CpRu(CH_3CN)$_3$][BAr_F] complex and 1,10-phenanthroline (2.5 mol% each). While the reaction was mostly unproductive, a product was isolated in low yield (<10%). This compound **3aA** presented interesting characteristics in ^{13}C-NMR and IR spectroscopy and an additional mass of 114.10 Da (equivalent to one carbene moiety).[10] In fact, data indicated a disappearance of the amide and the inclusion of two ketones and one ester functional groups; the pyrrolidine structure of **3aA** being determined with certainty by X-ray diffraction in the course of the study (see Figure 2).


1. Previous work (refs. 2 & 3)

2. This work

Scheme 1. Top: general reactivity of amides (lactams) with diazo carbonyl derivatives under metal catalysis. Bottom: Copper-mediated condensation of ester diazo derivatives with γ-aryl lactams and subsequent pyrrolizidine formation.

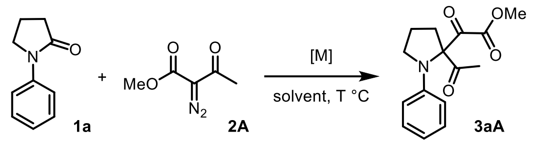
Encouraged by this finding, conditions for the exclusive formation of **3aA** were looked for. In diazo decomposition chemistry, reactivity is often controlled by the nature of the metal catalyst.[1] Experiments were thus performed with dirhodium and copper complexes.[11] The results are summarized in Table 1. While $Rh_2(Oct)_4$ and $Rh_2(esp)_2$ complexes were ineffective (entries 2 and 3), promising results were obtained with $Cu(acac)_2$ and $Cu(hfacac)_2$ (27% and 32% of **3aA** respectively, entries 4 and 5).[12] Using an excess of lactam **1a** over diazo **2A**, a similar reactivity but a cleaner crude reaction mixture was obtained (30% of **3aA**, entry 6).[13] $Cu(acac)_2$ and other copper sources were then tested at 100 °C in 1,2-dichloroethane (DCE) for longer reaction

---

[*] Dr. S. Goudedranche, L. Egger, Prof. J. Lacour
Département de Chimie Organique, Université de Genève
quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)
Fax: (+41) 22-379-3215
E-mail: jerome.lacour@unige.ch
Homepage: http://www.unige.ch/sciences/chiorg/lacour/
Dr. C. Besnard,
Laboratoire de Cristallographie, Université de Genève
quai Ernest Ansermet 24, 1211 Geneva 4 (Switzerland)

times (entries 7-10). Copper iodide led to the best result (62%), which was further improved by decreasing the concentration (0.13 *vs.* 0.53 M, entry 11). An isolated yield of 74% was obtained for **3aA** under these conditions, which were selected for the continuing studies.[14],[15]

Table 1. Optimization study[a]



Entry	Catalysts	mol%	**1**:**2** ratio	Solv.	T [°C]	Time [h]	Yields [%]
1[b]	[CpRu]	2.5	0.5	DCM	60	3	<10
2	$Rh_2(Oct)_4$	1.0	0.5	DCM	60	3	0
3	$Rh_2(esp)_2$	1.0	0.5	DCM	60	3	0
4	$Cu(acac)_2$	10	0.5	DCM	60	3	27
5	$Cu(hfacac)_2$	10	0.5	DCM	60	3	32
6	$Cu(acac)_2$	10	3.0	DCM	60	3	30
7	$Cu(acac)_2$	10	3.0	DCM	100	3	44
8	CuTc	10	3.0	DCE	100	24	42
9	CuBr	10	3.0	DCE	100	24	49
10	CuI	10	3.0	DCE	100	24	62
11[c]	CuI	10	3.0	DCE	100	24	77(74)

[a] Reactions performed in sealed vials at 0.53 M concentration of limiting reagents. Yields determined by ^{1}H NMR spectroscopy with phenyltrimethylsilane as internal standard. [b] 2.5 mol% of [CpRu(CH$_3$CN)$_3$][BAr$_F$] and 1,10-phenanthroline were used. [c] 0.13 M concentration of **2A** as limiting reagent. Isolated yield in parenthesis.

The reaction was then performed with a variety of γ-lactams.[16] The results are presented in Figure 1. Using *p*-substituted substrates, reactions occurred with both electron-donating (EDG) and electron-withdrawing groups (EWG) on the aryl moiety to give **3bA-3gA**. Product **3bA** (*p*-OMe, 78%) was found to be moderately soluble in heptane and a slow diffusion into a DCM solution afforded X-ray quality crystals. As shown by the structural analysis (Figure 2, left), **3bA** is characterized by a pyrrolidine core and a functionalized α-pseudoquaternary center carrying acetyl and 2-oxoethanoate side chains; this structure fitting all spectroscopic data recorded. For the isolation of *m*-substituted products **3hA-3jA** and bis-substituted **3kA-3lA**, it was necessary to use EWG at *meta* positions.[17] Ring substituted pyrrolidinones were also engaged. Spiro **3mA** was readily obtained (63%). For the other products containing additional stereogenic center(s), diastereomers were expected. While **3nA** and **3oA** were generated with a rather low diastereoselectivity (*d.r.* 3:1 and 5:1 respectively), ^{1}H-NMR analysis (400 MHz) of crude mixtures of **3pA** and bicyclic **3qA** indicated the presence of single stereoisomers (*d.r.* > 20:1). For **3oA** and **3qA**, the relative configuration of the major (single) diastereomer was established by X-ray diffraction analysis.[18] With **3pA**, the reaction was performed with racemic and enantiopure substrates; the product being formed not only as a single diastereomer but also as a single enantiomer in the latter case (enantiospecificity, *es* > 99%). Finally, substrates with β- and α-naphthyl groups on the N-atom were utilized. Pyrrolizidines **4rA** and **4sA** were directly obtained; the structures of which being confirmed by X-ray diffraction analyses (eg, **4rA**: Figure 2, right). The origin of these products will be later explained.

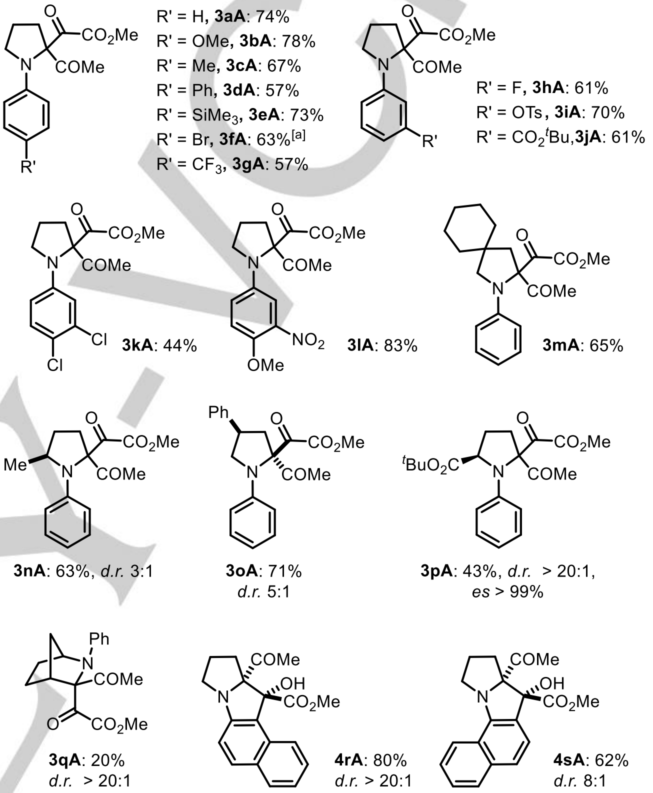


Figure 1. Pyrrolidines **3bA**-**3qA** and pyrrolizidines **4rA**-**4aA**.[a] For the formation of **3fA**, 20 mol% of CuI were necessary.

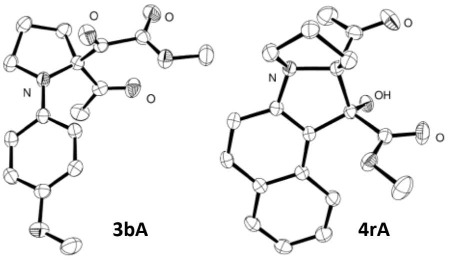


Figure 2. ORTEP views of pyrrolidine **3bA** and pyrrolizidine **4rA**. Oxygen atoms of the carbonyl and hydroxyl groups are indicated. H-atoms are omitted for clarity.

Then, a variety of diazo reagents was reacted with *N*-phenyl 2-pyrrolidinone **1a**. The results are summarized in Figure 3. First, using methyl diazobutyroacetate (R = ^{n}Pr instead of Me), product **3aB** was obtained in a rather low yield (24 %). Care was then taken to react preferentially acetyl diazo reagents to yield products **3aC**-**3aK** in moderate to good yields (30-82%). The transformation is general with the acetyl group always connected to the pseudoquaternary center in these products **3**. The ester side chains R' can be linear or cyclic, functionalized or not. In the case of **3aG** and **3aI**, the lower yields (30-31%) can be ascribed to steric hindrance (R' = 1-adamantyl) on one hand and to competing intramolecular cyclopropanation reactivity (R' = allyl) on the other. Using α-diazo β-ketoamide and β-phosphorylester reagents, pyrrolidines **3aL** and **3aM** were obtained in 25% and 60% respectively. The formation of the products can be rationalized by a preferred migration of the acetyl and phosphoryl groups respectively (see the mechanistic discussion, *vide infra*). Interestingly, diazomalonates reacted also well under the reaction conditions. With symmetrical reagents, pyrrolidines **3aN**-**3aP** were obtained (52-75%); smaller methyl substituents being favorable over *tert*-butyl groups for the yield. In the case of unsymmetrical reagents, mixtures of regioisomers were observed in the crude (^{1}H-NMR, 400 MHz). The regioselectivity was maximum with the *tert*-butyl methyl diazomalonate reagent (product **3aS**, *r.r.* 5.2:1). The major isomer corresponds to the migration of the more hindered fragment (R' = ^{t}Bu).

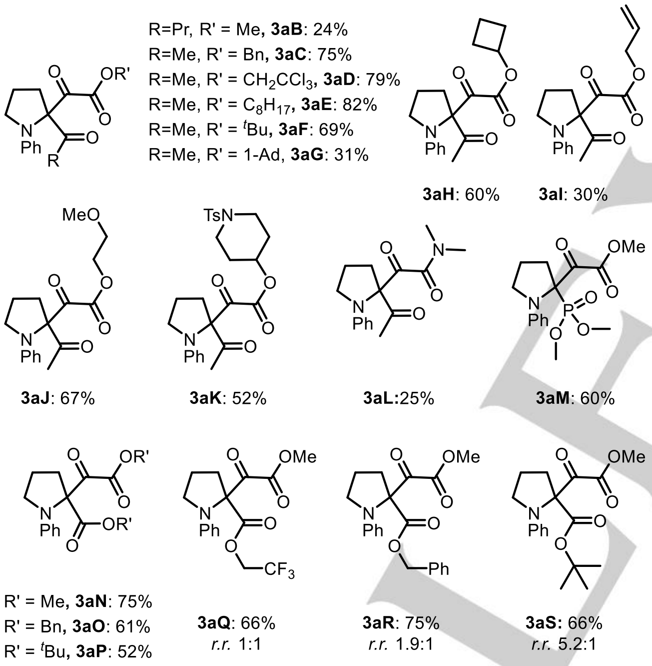
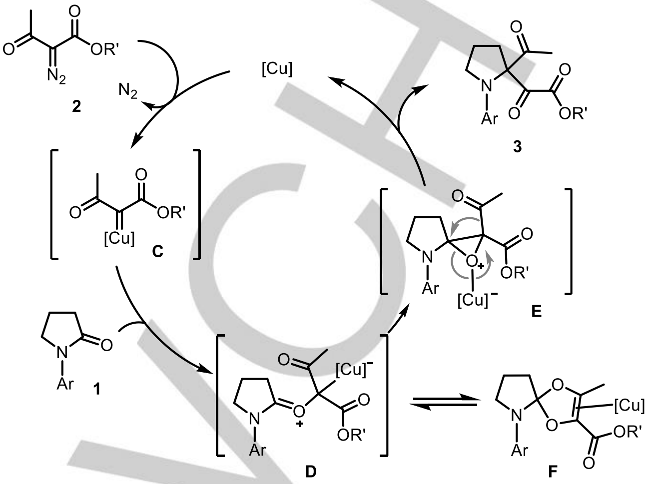


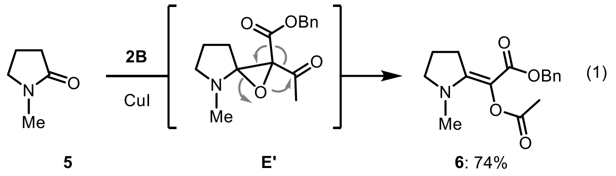
Figure 3. Pyrrolidines **3aC**-**3aS**.

A mechanistic rationale coherent with the results is proposed in Scheme 2. First, a copper-catalyzed decomposition of diazo reagents **2** generates metal carbene intermediates **C**. Then, nucleophilic attacks of lactams **1** form metal carbonyl ylides **D**. Promoted by the proximity and by the electrophilic activation, an intramolecular addition occurs and yields epoxides **E**; this type of strained moieties is often evoked in carbonyl ylide chemistry.[1] *In fine*, a [1,2]-migration happens to form the pyrrolidine skeleton and the appendant side-chains.[19] This step (**E** → **3**) can be either concerted or stepwise.[20] It also involves, when an option is possible, the preferred migration of the one of the two groups linked originally to the diazo moiety. Clearly, in view of the results, acyl (or phosphoryl) groups migrate better than esters (or amides).[20-21] When two esters are involved, the [1,2]-migration still occurs. With unsymmetrical malonate derivatives, the regioselectivity is then rather low (*r.r.* 1:1 to 5.2:1).[22]



Scheme 2. Mechanistic rationale.

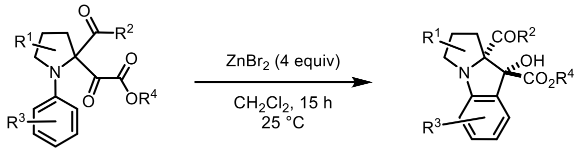
Additionally, the formation of spiro intermediates of type **F** cannot be ruled out (Scheme 4).[23] Step (**D** ⇆ **F**) would be an equilibrium and compounds **F** would be considered as a "reservoir" if the following step (**D** → **E**) would be relatively slow. Also, a validation for the formation of epoxide intermediates **E** can be found in the reactivity of *N*-methyl γ-lactam **5** (eq. 1). Under the reaction conditions, this substrate leads to amino acetate enol ether **6** in 74% yield. The formation of **6** is best rationalized by a [1,2]-migration of the acyl group of **E'** to the oxygen atom rather than the α-carbon. The resemblance of this pathway to that occurring in the presence of silyl substituents is striking.[3] It is favored by the electron-rich nature of the methyl-substituted nitrogen that helps cleave the epoxide in the direction of the enolate formation.



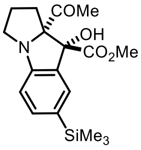
Finally, a generalization of the reactivity observed for **4rA** and **4sA** (Figure 1) was looked for. These products clearly result, after pyrrolidine formation, from subsequent Friedel–Crafts reactions onto the naphthyl moieties. Compounds **3eA**, **3oA**, **3aC** and **3aN** were thus treated with $ZnBr_2$ (4.0 equiv) in CH_2Cl_2. In the presence of the *Lewis* acid, ring closures occurred to yield the corresponding pyrrolizidines (90-96%, Table 2). The diastereoselectivity is excellent, even for **4oA**. In this case, the 5:1 ratio reflects the original diastereomeric purity of pyrrolidine **3oA** and not a lack of selectivity in the ring closure. The relative configuration of the major diastereomers of **4oA** and **4aN**, determined by structural analysis, matches that observed for **4rA** and **4sA**.

In conclusion, a new reactivity is reported for metal carbene reactions of *N*-aryl γ-lactams **1** owing to the combination of acceptor-acceptor diazo reagents and copper catalysis. Novel pyrrolidine motifs of type **3** are obtained as (usually) single regioisomers. A preferred [1,2]-migration of acyl or phosphoryl groups is observed for the formation of the functionalized α-pseudoquaternary centers. Further applications of this approach are developed as pyrrolidines **3** and pyrrolizidines **4** are common motifs in medicinal chemistry and potentially biologically relevant natural products respectively.[7]

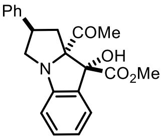
Table 2. Pyrrolizidine synthesis.[a]



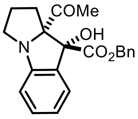
3 **4**



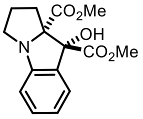
(1) **4eA**: 96%
d.r. > 20:1



(2) **4oA**: 90%
d.r. 5:1[b]



(3) **4aC**: 95%
d.r. > 20:1



(4) **4aN**: 95%
d.r. 18:1

[a] Reaction conditions: pyrrolidine **3** (0.1 mmol) and $ZnBr_2$ (0.4 mmol), were stirred in CH_2Cl_2 (1 mL) at 25 °C for 15 h. Isolated yields of compounds **4** as average of at least two reactions. [b] The 5:1 ratio reflects the original diastereomeric purity of pyrrolidine **3oA** and not the selectivity of the reaction.

Experimental Section

Synthetic procedures and spectral characterization of new compounds **1**-**4** are reported in the electronic supporting information. CCDC 1497636-1497641, products **3bA**, **3qA**, **4aN**, **4oA**, **4rA** and **4sA**, contain 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.

Acknowledgements

We thank the University of Geneva and the Swiss NSF for financial support. We also acknowledge the contributions of the Sciences Mass Spectrometry (SMS) platform at the Faculty of Sciences, University of Geneva.

Keywords: acceptor-acceptor diazo reagents • [1,2]-acyl migrations • carbonyl ylide • γ-lactams • metal carbenes • pyrrolidines • pyrrolizidines

[1] a) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981-10080; b) D. M. Hodgson, A. H. Labande, S. Muthusamy, in *Organic Reactions*, John Wiley & Sons, Inc., **2013**; c) A. Padwa, *Chem. Soc. Rev.* **2009**, *38*, 3072-3081.

[2] a) D. M. Hodgson, C. Villalonga-Barber, J. M. Goodman, S. C. Pellegrinet, *Org. Biomol. Chem.* **2010**, *8*, 3975-3984; b) D. B. England, A. Padwa, *J. Org. Chem.* **2008**, *73*, 2792-2802; c) D. B. England, A. Padwa, *Org. Lett.* **2007**, *9*, 3249-3252; d) J. M. Mejía-Oneto, A. Padwa, *Org. Lett.* **2006**, *8*, 3275-3278; e) A. Padwa, S. M. Lynch, J. M. Mejía-Oneto, H. Zhang, *J. Org. Chem.* **2005**, *70*, 2206-2218 and references therein.

[3] a) G. S. Nandra, P. S. Pang, M. J. Porter, J. M. Elliott, *Org. Lett.* **2005**, *7*, 3453-3455; b) D. L. Priebbenow, C. Bolm, *RSC Advances* **2013**, *3*, 10318-10322.

[4] This type of reactivity also occur with thioamides, see: N. D. Koduri, Z. Wang, G. Cannell, K. Cooley, T. M. Lemma, K. Miao, M. Nguyen, B. Frohock, M. Castaneda, H. Scott, D. Albinescu, S. R. Hussaini, *J. Org. Chem.* **2014**, *79*, 7405-7414.

[5] For references involving diazodicarbonyls, see: a) C. Zhu, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2016**, *55*, 11867-11871; b) E. T. Satumov, J. J. Medvedev, D. I. Nilov, M. A. Sandzhieva, I. A. Boyarskaya, V. A. Nikolaev, A. V. Vasilyev, *Tetrahedron* **2016**, *72*, 4835-4844; c) H. Wada, H. E. L. Williams, C. J. Moody, *Angew. Chem., Int. Ed.* **2015**, *54*, 15147-15151; d) H. Nur Kubilay, F. Seyma Gungor, O. Anac, *Helv. Chim. Acta* **2015**, *98*, 1245-1253; e) J. J. Medvedev, M. V. Meleshina, T. L. Panikorovskii, C. Schneider, V. A. Nikolaev, *Org. Biomol. Chem.* **2015**, *13*, 9107-9117; f) K. E. Coffey, G. K. Murphy, *Synlett* **2015**, *26*, 1003-1007; g) F. Urabe, S. Miyamoto, K. Takahashi, J. Ishihara, S. Hatakeyama, *Org. Lett.* **2014**, *16*, 1004-1007; h) P. M. Truong, P. Y. Zavalij, M. P. Doyle, *Angew. Chem., Int. Ed.* **2014**, *53*, 6468-6472; i) R. P. Pandit, Y. R. Lee, *Org. Biomol. Chem.* **2014**, *12*, 4407-4411; j) M. D. Mandler, P. M. Truong, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2014**, *16*, 740-743; k) A. Sharma, C. Besnard, L. Guénée, J. Lacour, *Org. Biomol. Chem.* **2012**, *10*, 966-969; l) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 15497-15504; m) A. Sharma, L. Guénée, J.-V. Naubron, J. Lacour, *Angew. Chem. Int. Ed.* **2011**, *50*, 3677-3680; n) J. Linder, T. P. Garner, H. E. L. Williams, M. S. Searle, C. J. Moody, *J. Am. Chem. Soc.* **2011**, *133*, 1044-1051; o) J. F. Briones, H. M. L. Davies, *Tetrahedron* **2011**, *67*, 4313-4317; p) I. F. Clemencon, B. Ganem, *Tetrahedron* **2007**, *63*, 8665-8669; q) G. A. Moniz, J. L. Wood, *J. Am. Chem. Soc.* **2001**, *123*, 5095-5097

[6] For previous pyrrolidine syntheses involving diazo reagents, see: a) S. M. Nicolle, W. Lewis, C. J. Hayes, C. J. Moody, *Angew. Chem. Int. Ed.* **2016**, *55*, 3749-3753; b) I. Rodriguez, M. I. Calaza, A. I. Jimenez, C. Cativiela, *New J. Chem.* **2015**, *39*, 3310-3318; c) J. J. Medvedev, O. S. Galkina, A. A. Klinkova, D. S. Giera, L. Hennig, C. Schneider, V. A. Nikolaev, *Org. Biomol. Chem.* **2015**, *13*, 2640-2651; d) K. Liu, C. Zhu, J. Min, S. Peng, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 12962-12967; e) C. Jing, D. Xing, L. Gao, J. Li, W. Hu, *Chem. Eur. J.* **2015**, *21*, 19202-19207; f) A. C. B. Burtoloso, R. M. P. Dias, B. Bernardim, *Acc. Chem. Res.* **2015**, *48*, 921-934; g) A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei, C.-M. Che, *Angew. Chem. Int. Ed.* **2014**, *53*, 14175-14180; h) C. Jing, D. Xing, W. Hu, *Chem. Commun.* **2014**, *50*, 951-953; i) L. Jiang, R. Xu, Z. Kang, Y. Feng, F. Sun, W. Hu, *J. Org. Chem.* **2014**, *79*, 8440-8446; j) C. Jing, D. Xing, Y. Qian, T. Shi, Y. Zhao, W. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 9289-9292; k) T. M. Bott, J. A. Vanecko, F. G. West, *J. Org. Chem.* **2009**, *74*, 2832-2836; l) C. J. Hayes, A. E. Sherlock, M. P. Green, C. Wilson, A. J. Blake, M. D. Selby, J. C. Prodger, *J. Org. Chem.* **2008**, *73*, 2041-2051; m) Q.-H. Deng, H.-W. Xu, A. W.-H. Yuen, Z.-J. Xu, C.-M. Che, *Org. Lett.* **2008**, *10*, 1529-1532; n) F. A. Davis, Y. Wu, H. Xu, J. Zhang, *Org. Lett.* **2004**, *6*, 4523-4525; o) E. Roberts, J. P. Sançon, J. B. Sweeney, J. A. Workman, *Org. Lett.* **2003**, *5*, 4775-4777.

[7] a) J. Robertson, K. Stevens, *Nat. Prod. Rep.* **2014**, *31*, 1721-1788; b) E. V. Prusov, *Angew. Chem. Int. Ed.* **2014**, *53*, 6037-6037.

[8] a) T. Achard, C. Tortoreto, A. I. Poblador-Bahamonde, L. Guénée, T. Bürgi, J. Lacour, *Angew. Chem. Int. Ed.* **2014**, *53*, 6140-6144; b) M. Vishe, R. Hrdina, L. Guénée, C. Besnard, J. Lacour, *Adv. Synth. Catal.* **2013**, *355*, 3161-3169; c) C. Tortoreto, T. Achard, W. Zeghida, M. Austeri, L. Guénée, J. Lacour, *Angew. Chem. Int. Ed.* **2012**, *51*, 5847-5851; d) R. Ballesteros-Garrido, D. Rix, C. Besnard, J. Lacour, *Chem. Eur. J.* **2012**, *18*, 6626-6631; e) D. Rix, R. Ballesteros-Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2011**, *50*, 7308-7311; f) W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2010**, *49*, 7253-7256.

[9] a) C. Tortoreto, T. Achard, L. Egger, L. Guénée, J. Lacour, *Org. Lett.* **2016**, *18*, 240-243; b) M. Austeri, D. Rix, W. Zeghida, J. Lacour, *Org. Lett.* **2011**, *13*, 1394-1397.

[10] Signals at 209.3, 195.7, 164.5 ppm in ^{13}C NMR and frequencies at 1734, 1710, 1599 cm^{-1} in IR.

[11] a) X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162-10173; b) B. Schmidt, *Angew. Chem. Int. Ed.* **2005**, *44*, 3802-3803.

[12] a) M. E. Alonso, M. d. C. Garcia, A. W. Chitty, *J. Org. Chem.* **1985**, *50*, 3445-3449; b) M. E. Alonso, A. W. Chitty, *Tetrahedron Lett.* **1981**, *22*, 4181-4184.

[13] An excess of diazo reagent is detrimental due, probably, to a reactivity of the resulting carbene with the keto group of **3aA**. See reference 9.

[14] In all these experiments, reactions were performed in sealed vials. Slow addition (2 h) of diazo **2A** at reflux of DCE under CuI catalysis did not improve the reaction.

[15] In this study and later, reactions were typically performed with 0.16 mmol of diazo reagent. On a 1.6 mmol scale of **2A**, product **3aA** was isolated in 65% yield (285 mg).

[16] Currently, under optimized reaction conditions, N-aryl β- and δ-lactams either decompose or react to yield several products in low yield.

[17] For instance, to obtain **3iA** (70%), it was necessary to transform the hydroxyl group into a tosyl moiety. Otherwise, direct formation of the corresponding pyrrolizidine of type 4 occured.

[18] The relative configuration of the major diastereomer of **3oA** was deduced from the structure of **4oA**. See the supporting information.

[19] In reference 3, the TMS group was migrating to the oxygen atom to generate enol ethers. Herein, a preferred migration to the electrophilic carbon is noted.

[20] L. Wang, X. Xie, Y. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13302-13306.

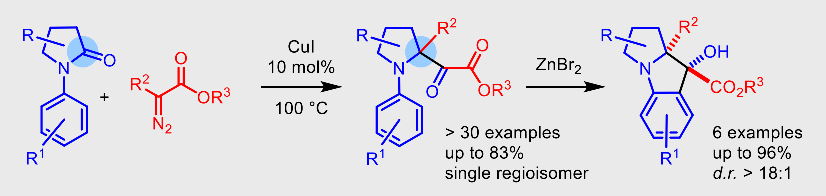
[21] For leading references on [1,2]-acyl migrations, see: a) E. Hasegawa, S. Arai, E. Tayama, H. Iwamoto, *J. Org. Chem.* **2015**, *80*, 1593-1600; b) Q.-Y. Meng, T. Lei, L.-M. Zhao, C.-J. Wu, J.-J. Zhong, X.-W. Gao, C.-H. Tung, L.-Z. Wu, *Org. Lett.* **2014**, *16*, 5968-5971; c) W. Fan, P. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 12201-12204; d) Y. Xiong, S. E. Schaus, J. A. Porco, *Org. Lett.* **2013**, *15*, 1962-1965; e) A. I. Tsai, C.-P. Chuang, *Tetrahedron* **2008**, *64*, 5098-5102; f) C. Le Drian, P. Vogel, *Helv. Chim. Acta* **1987**, *70*, 1703-1720; g) C. Le Drian, P. Vogel, *Tetrahedron Lett.* **1987**, *28*, 1523-1525; h) R. C. Klix, R. D. Bach, *J. Org. Chem.* **1987**, *52*, 580-586; i) M. Campbell, M. Sainsbury, R. West, *Tetrahedron Lett.* **1987**, *28*, 3865-3868; j) J. R. Williams, G. M. Sarkisian, J. Quigley, A. Hasiuk, R. VanderVennen, *J. Org. Chem.* **1974**, *39*, 1028-1032; k) S. P. Singh, J. Kagan, *J. Am. Chem. Soc.* **1969**, *91*, 6198-6199; l) D. J. Collins, *J. Chem. Soc.* **1959**, 3919-3928; m) H. O. House, D. J. Reif, *J. Am. Chem. Soc.* **1957**, *79*, 6491-6495 and references therein.

[22] In the case of product **3aS** (*r.r.* 5.2:1), the preferred migration of the tert-butyl ester fragment could be rationalized by the stronger donor character of the *tert*-butyl (vs. methyl) group.

[23] This reaction would be analogous to that observed with lactones and cyclic carbonates. See reference 9.

Entry for the Table of Contents

COMMUNICATION



From C=O to CR$_2$: In the context of γ-lactam chemistry, functionalized pyrrolidines carrying α-pseudoquaternary centers are readily prepared by condensations with acceptor-acceptor diazo reagents under Cu-catalysis. Thanks to preferred [1,2]-acyl or phosphoryl group migrations, single regioisomers are generated. Moreover, tricyclic pyrrolizidines can be obtained in excellent yields and diastereoselectivity.

*S. Goudedranche, C. Besnard, L. Egger, J. Lacour**

Page No. – Page No.

Synthesis of pyrrolidines and pyrrolizidines with α-pseudoquaternary centers by Cu-catalyzed condensation of α-diazodicarbonyls and aryl γ-lactams