Metal Carbenes

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

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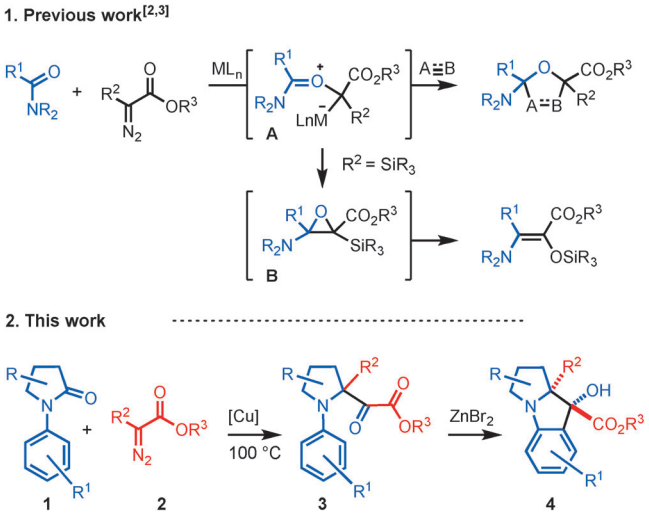
Abstract: *N-aryl γ-lactams react intermolecularly with acceptor–acceptor diazo reagents, usually dicarbonyl compounds, in a copper-catalyzed process to yield functionalized pyrrolidines with α-pseudoquaternary centers. As 1,2-acyl or -phosphoryl migration is preferred, single regioisomers are obtained. Furthermore, in the presence of a Lewis acid, subsequent Friedel–Crafts reactions yield tricyclic pyrrolizidines in excellent yields (90–96 %) and diastereoselectivities (up to >20:1).*

Tertiary amides and lactams are known to react with diazoester 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 in intramolecular reactions.[2] Of interest for the current study, when silyl substituents are present on the diazo reagent, epoxide intermediates **B** are formed, which, after silyl group migration, are transformed into amino silyl enol ethers.[3,4] Herein, the intermolecular reactivity of *N*-aryl γ-lactams **1** with α-diazodicarbonyl compounds **2** is reported (Scheme 1, bottom).[5] Highly functionalized pyrrolidines **3** with α-pseudoquaternary centers are obtained in good yields (up to 83 %).[6] In fact, amide groups are transformed into amines with adjacent acetyl and 2-oxoethanoate chains in one step. This transformation, which involves acyl (or phosphoryl) group migration, proceeds with very high regioselectivity and is specifically catalyzed by copper salts (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 selectivities (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, for example, in peptide or medical chemistry, with their preparation by other routes being difficult to imagine.



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

Recently, metal-catalyzed decompositions of acceptor–acceptor α-diazodicarbonyl reagents have been studied by our group to afford an extended range of reactivities in the presence of Lewis bases.[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 these transformations involving carbonyl ylide intermediates, reactions of diazodicarbonyl 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 rather unproductive, a product was isolated in low yield (<10 %). This compound, **3aA**, presented interesting characteristics in ^{13}C NMR and IR spectroscopy, and an increase in molecular mass of 114.10 Da (equivalent to one carbene moiety).[10] In fact, data indicated the disappearance of the amide and the presence of two ketones and one ester functional group; the pyrrolidine structure of **3aA** was finally confirmed by X-ray diffraction in the course of the study (see Figure 2).

Encouraged by this finding, we searched for conditions that enable the exclusive formation of **3aA**. In diazo decomposition chemistry, reactivity is often controlled by

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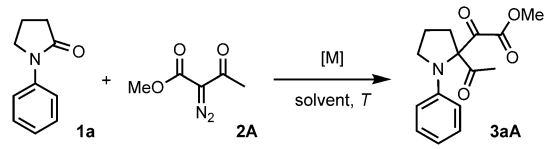
Table 1: Optimization study.[a]



Entry	Catalyst (mol%)	**1**/**2** ratio	Solvent	T [°C]	*t* [h]	Yield [%]
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 the limiting reagent. Yields determined by ^{1}H NMR spectroscopy with phenyltrimethylsilane as an internal standard. Yields of isolated products are given in parentheses. [b] 2.5 mol% of $[CpRu(CH_3CN)_3][BAr_F]$ and 1,10-phenanthroline were used. [c] **2A** as the limiting reagent (0.13 M). acac = acetylacetonate, Cp = cyclopentadienyl, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, hfacac = hexafluoroacetylacetonate, Tc = thiophene-2-carboxylate.

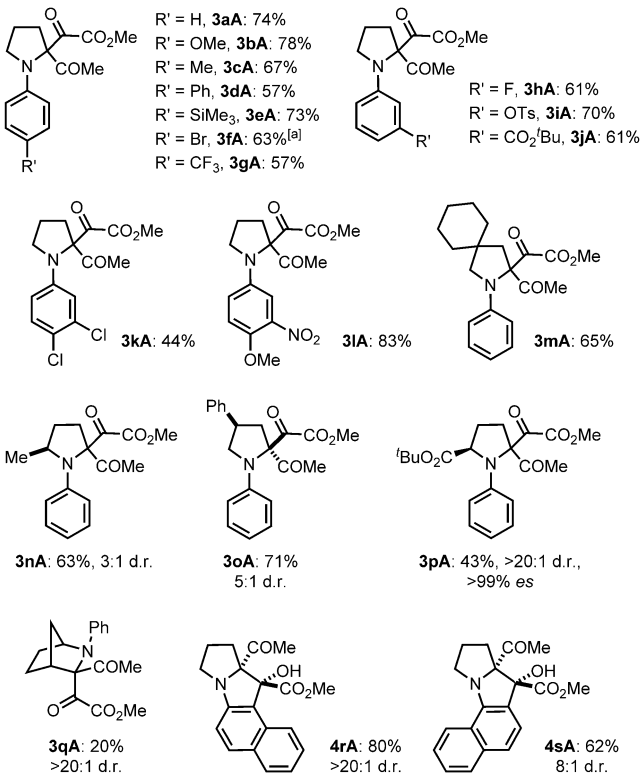


Figure 1. Synthesis of pyrrolidines **3bA**–**3qA** and pyrrolizidines **4rA**–**4aA**. For the reaction conditions, see Table 1, entry 11. [a] For the formation of **3fA**, 20 mol% of CuI were necessary.

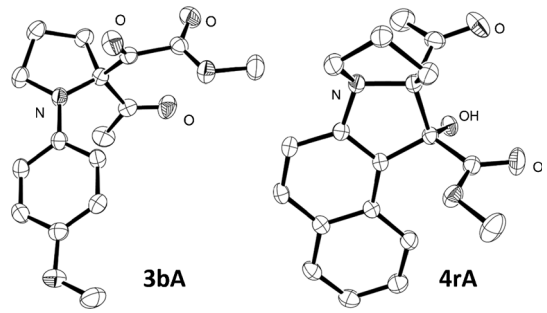


Figure 2. ORTEP views of pyrrolidine **3bA** and pyrrolizidine **4rA**. Thermal ellipsoids set at 50% probability. The O atoms of the carbonyl and hydroxy groups are indicated. H atoms omitted for clarity.

the nature of the metal catalyst.[1] Experiments were thus performed with dirhodium and copper complexes (Table 1).[11] Whereas $Rh_2(oct)_4$ 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** relative to diazo substrate **2A**, similar reactivity was observed, 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 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). **3aA** was isolated in 74% yield under these conditions, which were selected for further studies.[14,15]

A variety of γ-lactams were then subjected to these reaction conditions (Figure 1).[16] With *para*-substituted substrates, the reactions worked well with both electron-donating (EDG) and electron-withdrawing (EWG) groups on the aryl moiety to give **3bA**–**3gA**. Product **3bA** (*p*-OMe, 78%) was found to be moderately soluble in heptane, and slow diffusion into a DCM solution afforded crystals suitable for X-ray crystallography. As shown by the structural analysis (Figure 2, left), **3bA** features a pyrrolidine core and a functionalized α-pseudoquaternary center carrying acetyl and 2-oxoethanoate side chains; this structure is in agreement with all recorded spectroscopic data. For the isolation of the *meta*-substituted products **3hA**–**3jA** and bis-substituted **3kA**–**3lA**, EWG groups in the *meta* position were necessary.[17] Ring-substituted pyrrolidinones were also used as substrates, and spiro compound **3mA** was readily obtained (65%). For the other products containing additional stereogenic center(s), the formation of diastereomers was expected. Whereas **3nA** and **3oA** were generated with rather low diastereoselectivity (3:1 and 5:1 d.r., respectively), ^{1}H NMR analysis (400 MHz) of crude mixtures of **3pA** and bicyclic **3qA** indicated the presence of only one diastereomer (>20:1 d.r.). For **3oA** and **3qA**, the relative configuration of the major (single) diastereomer was established by X-ray diffraction.[18] The synthesis of **3pA** was performed with racemic and enantiopure substrate; the product was 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 nitrogen atom were utilized. Pyrrolizidines **4rA** and **4sA** were directly obtained; their

structures were again confirmed by X-ray diffraction (see Figure 2, right for the structure of **4rA**). The formation of these products is explained later.

Then, a variety of diazo reagents were reacted with *N*-phenyl 2-pyrrolidinone (**1a**; Figure 3). First, using methyl

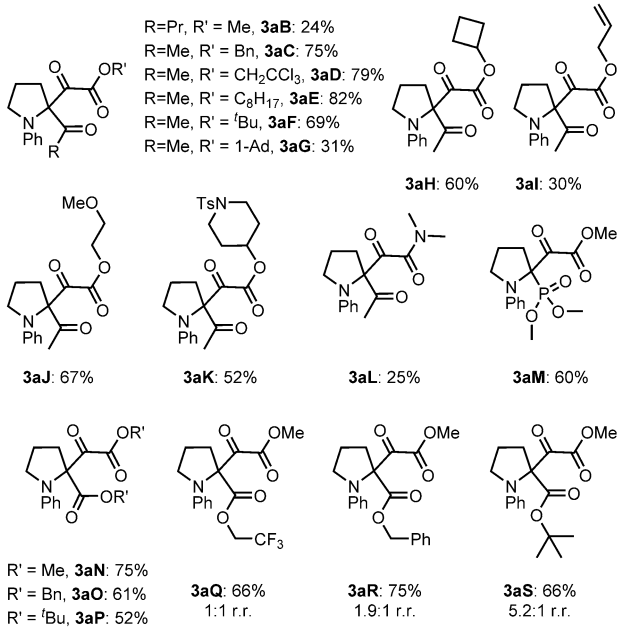
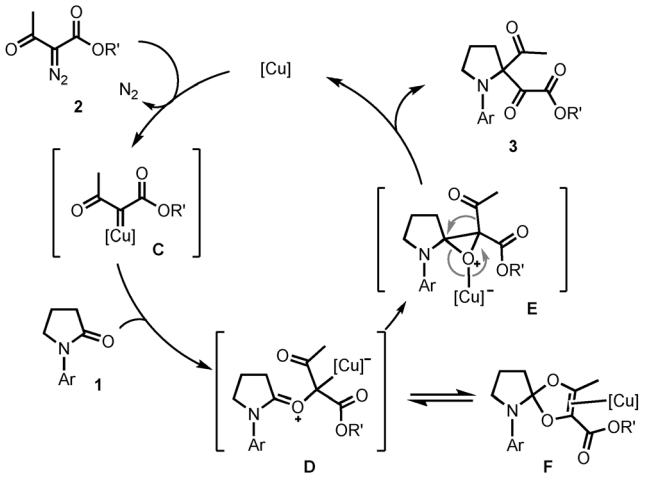


Figure 3. Synthesis of pyrrolidines **3aC–3aS**. For the reaction conditions, see Table 1, entry 11.

diazobutyroacetate (R = ^{n}Pr instead of Me), product **3aB** was obtained in rather low yield (24%). Care was then taken to preferentially react acetyl diazo reagents to yield products **3aC–3aK** in moderate to good yields (30–82%). The transformation is general with the acetyl group always attached to the pseudoquaternary center in these products **3**. The ester side chains R′ can be linear or cyclic, functionalized or not. For **3aG** and **3aI**, the lower yields (31 and 30%) were ascribed to steric hindrance (R′ = 1-adamantyl) in the first reaction and to competing intramolecular cyclopropanation (R′ = allyl) in the latter. Using α-diazo β-ketoamide and β-phosphoryl ester reagents, pyrrolidines **3aL** and **3aM** were obtained in 25% and 60%, respectively. The formation of these products can be rationalized by preferred migration of the acetyl and phosphoryl groups, respectively (see below). Interestingly, diazomalonates also reacted well under these reaction conditions. With symmetric reagents, pyrrolidines **3aN–3aP** were obtained (52–75%); smaller methyl substituents being favorable over *tert*-butyl groups for the yield. With unsymmetric reagents, mixtures of regioisomers were observed in the crude reaction mixture (^{1}H NMR analysis, 400 MHz). The regioselectivity was highest with *tert*-butyl methyl diazomalonate (product **3aS**, 5.2:1 r.r.). The major isomer corresponds to migration of the more hindered fragment (R′ = ^{t}Bu).

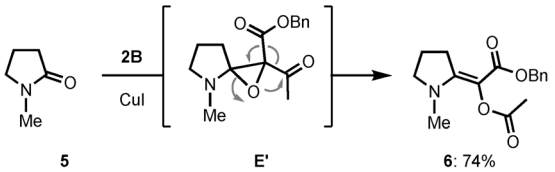
A mechanistic rationale coherent with these results is proposed in Scheme 2. First, copper-catalyzed decomposition of diazo reagent **2** generates metal carbene intermediate **C**. Then, nucleophilic attack of lactam **1** yields metal carbonyl ylide **D**. Promoted by the proximity and the electrophilic activation, an intramolecular addition occurs and yields epoxide **E**; such strained moieties are often evoked in carbonyl ylide chemistry.[1] Then, a 1,2-migration occurs to



Scheme 2. Mechanistic rationale.

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 this option is available, the preferred migration of one of the two groups originally attached 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 unsymmetric malonate derivatives, the regioselectivity is rather low (1:1 to 5.2:1 r.r.).[22]

Additionally, the formation of spiro intermediates of type **F** cannot be ruled out (Scheme 2).[23] This step (**D**⇄**F**) would be an equilibrium, and compound **F** could be considered as a "reservoir" if the following step (**D**→**E**) is relatively slow. The formation of epoxide intermediate **E** is also supported by the reactivity of *N*-methyl γ-lactam **5** [Eq. (1)]. Under the

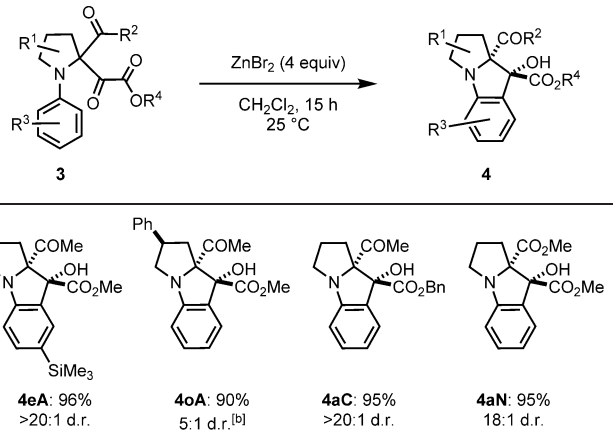


(1)

optimized reaction conditions, this substrate gave 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 atom. The resemblance of this pathway to that occurring in the presence of silyl substituents is striking (Scheme 1, top).[3] It is favored by the electron-rich nature of the methyl-substituted nitrogen atom, which helps cleave the epoxide in the direction of the enolate formation.

Finally, we looked for a generalization of the reactivity observed with **4rA** and **4sA** (Figure 1). 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 closure occurred to yield the corresponding pyrrolizidines (90–96%, Table 2). The diastereoselectivities

Table 2: Pyrrolizidine synthesis.[a]



[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. Yields of isolated compounds **4** are given as averages 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.

were 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 configurations of the major diastereomers of **4oA** and **4aN**, determined by structural analysis, match those observed for **4rA** and **4sA**.

In conclusion, we have reported a new mode of reactivity for metal carbene reactions of *N*-aryl γ-lactams **1** that is based on the combination of acceptor–acceptor diazo reagents and copper catalysis. Novel pyrrolidine motifs of type **3** were obtained as (usually) single regioisomers. 1,2-Acyl or -phosphoryl migration occurred preferentially to yield functionalized products with α-pseudoquaternary centers. Further applications of this approach are currently being developed as pyrrolidines **3** and pyrrolizidines **4** are common motifs in medicinal chemistry and potentially biologically relevant natural products.[7]

Experimental Section

For synthetic procedures and characterization data, see the Supporting Information. CCDC 1497636 (**3bA**), 1497637 (**3qA**), 1497638 (**4aN**), 1497639 (**4oA**), 1497640 (**4rA**), and 1497641 (**4sA**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Keywords: acyl migrations · diazo reagents · γ-lactams · 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*, Wiley, **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 Adv.* **2013**, *3*, 10318–10322.

[4] This type of reactivity is also observed 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 reactions involving diazodicarbonyl compounds, see: a) C. Zhu, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2016**, *55*, 11867–11871; *Angew. Chem.* **2016**, *128*, 12046–12050; 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; *Angew. Chem.* **2015**, *127*, 15362–15366; 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**, 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; *Angew. Chem.* **2014**, *126*, 6586–6590; 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; *Angew. Chem.* **2011**, *123*, 3761–3764; 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. Clémençon, 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; *Angew. Chem.* **2016**, *128*,

3813 – 3817; b) I. Rodríguez, 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; *Angew. Chem.* **2015**, *127*, 13154 – 13159; 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; *Angew. Chem.* **2014**, *126*, 14399 – 14404; 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; *Angew. Chem.* **2013**, *125*, 9459 – 9462; 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; *Angew. Chem.* **2014**, *126*, 6149 – 6149.

[8] a) T. Achard, C. Tortoreto, A. I. Poblador-Bahamonde, L. Guénée, T. Bürgi, J. Lacour, *Angew. Chem. Int. Ed.* **2014**, *53*, 6140 – 6144; *Angew. Chem.* **2014**, *126*, 6254 – 6258; 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; *Angew. Chem.* **2012**, *124*, 5949 – 5953; 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; *Angew. Chem.* **2011**, *123*, 7446 – 7449; f) W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem. Int. Ed.* **2010**, *49*, 7253 – 7256; *Angew. Chem.* **2010**, *122*, 7411 – 7414.

[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] Resonances at 209.3, 195.7, and 164.5 ppm in the ^{13}C NMR spectrum and bands at 1734, 1710, and 1599 cm^{-1} in the IR spectrum.

[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; *Angew. Chem.* **2005**, *117*, 3868 – 3869.

[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 probably owing to a reaction of the resulting carbene with the keto group of **3aA**; see Ref. [9].

[14] All of these reactions were performed in sealed vials. Slow addition (2 h) of diazo substrate **2A** to a reaction mixture in DCE at reflux under CuI catalysis did not improve the reaction.

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

[16] Currently, under the 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 hydroxy group into a tosyl moiety. Otherwise, the corresponding pyrrolizidine of type **4** was directly formed.

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

[19] In Ref. [3], the TMS group migrated to the oxygen atom to generate enol ethers. Herein, migration to the electrophilic carbon atom was preferred.

[20] L. Wang, X. Xie, Y. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 13302 – 13306; *Angew. Chem.* **2013**, *125*, 13544 – 13548.

[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; *Angew. Chem.* **2014**, *126*, 12397 – 12400; 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** (5.2:1 r.r.), 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 Ref. [9].

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Communications

Metal Carbenes

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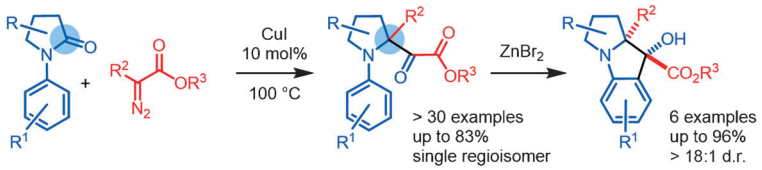
Synthesis of Pyrrolidines and Pyrrolizidines with α-Pseudoquaternary Centers by Copper-Catalyzed Condensation of α-Diazodicarbonyl Compounds and Aryl γ-Lactams



From C=O to CR_2: Functionalized pyrrolidines were readily prepared by condensation reactions of γ-lactams with acceptor–acceptor diazo reagents under copper catalysis. Preferential 1,2-acyl or -phosphoryl migration led to the formation of single regioisomers. These products could be further transformed into tricyclic pyrrolizidines in the presence of a Lewis acid.

