Advanced Synthesis & Catalysis

Accepted Article

Title: Acyl radical Addition onto Aza-Baylis-Hillman Adducts. A Stereocontrolled access to 2,3,5-Trisubstituted Pyrrolidines

Authors: Yannick LANDAIS, Simon Grélaud, Jonathan Lusseau, and Stéphane MASSIP

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700362

Link to VoR: http://dx.doi.org/10.1002/adsc.201700362

10.1002/adsc.201700362

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Acyl Radical Addition onto Aza-Baylis-Hillman Adducts. A Stereocontrolled Access to 2,3,5-Trisubstituted Pyrrolidines

Simon Grélaud,[a] Jonathan Lusseau,[a] Stéphane Massip,[b] and Yannick Landais[a]*

[a] Institute of Molecular Sciences, UMR-CNRS 5255, University of Bordeaux, 351 Cours de la libération, 33405 Talence cedex, France
[b] Institut Européen de Chimie et Biologie, 2, Rue Robert Escarpit, 33607 Pessac, France
Phone: (+33)-5 40 00 22 89; Fax : (+33)-5 40 00 62 86; e-mail: y.landais@ism.u-bordeaux1.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Free-radical addition of acyl radicals to chiral aza-Baylis-Hillman adducts was shown to afford the corresponding 1,4-aminoketones in good yields and good 1,2-stereocontrol. These ketones were then elaborated further using conditions varying as a function of the nature of the N-protecting group. Robust N-Ts protection thus allowed the formation, under acidic conditions, of a cyclic iminium which was reduced using bulky $(Me_3Si)_3SiH$ into the corresponding 2,3,5-pyrrolidine exhibiting a *trans-trans* relative configuration. In contrast, under these conditions, the N-Boc protecting group was removed, leading to the formation of stable dihydropyrroles, which were then hydrogenated with PtO_2, leading to 2,3,5-pyrrolidines having a *trans-cis* relative configuration. When additional ketone or ester groups were present on the pyrrolidine skeleton, further cyclization led to indolizidinones and pyrrolizidines in good overall yield in 4 steps and two-pot operations.

Keywords: Radicals; Acyl; Aza-Baylis-Hillman reaction; Indolizidines; pyrrolizidines

Introduction

Pyrrolidines, pyrrolizidines and indolizidines are very common nitrogen heterocycles in nature,[1] present in a large number of alkaloids isolated from leguminous plants but also secretions of small batrachians, ants or butterflies, which use these nitrogenous poisons as chemical defence against predators (Figure 1).[1a-b,1f] Polyhydroxyl analogues, including castanospermine or swainsonine have attracted much interest because of their glycosidase inhibitory activities and their potential use in the treatment against cancer and the HIV virus.[2] Since these nitrogen cycles are ubiquitous in nature, a great number of methodological studies has been devoted to their synthesis.[3] Among the most effective synthetic strategies, however, mention may be made of stereocontrolled cycloadditions from nitrones,[3a-d] intramolecular haloamidation reactions of olefins[3e-f] or transition metal-catalyzed olefin amidation.[3h-i] In this context, free-radical approaches have also been reported and holds a special place, allowing the efficient construction of complex nitrogen heterocycles of various ring size, using for instance cascade processes, under conditions which are compatible with resident functional groups.[3l-p]

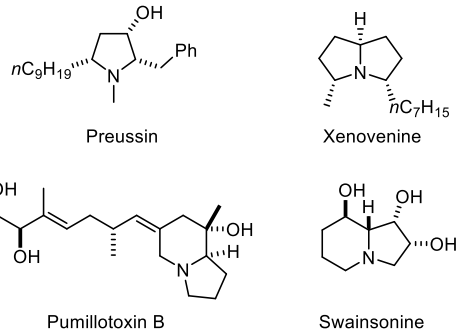
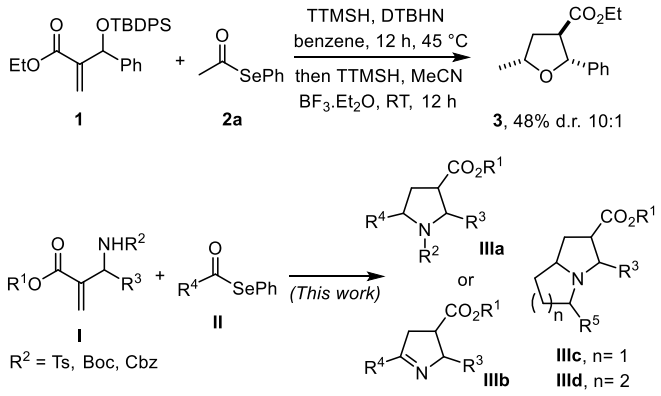


Figure 1. Naturally occurring pyrrolidines, pyrrolizidines and indolizidines.

Recently, our laboratory has developed a novel free-radical approach toward the oxygenated analogs, *i.e.* tetrahydrofurans such as **3**, based on a sequence featuring: (1) a stereocontrolled addition of an acyl radical, generated from the corresponding selenoester **2a**, to Baylis-Hillman adduct **1**, followed by (2) a one-pot desilylation/acetalization and (3) a reduction of the oxonium generated *in situ* under acid conditions (Scheme 1).[4] The three steps, which can be carried out in a single pot, proceed with excellent 1,2- and 1,3-diastereocontrol in the presence of $(Me_3Si)_3SiH$ (TTMSH),[5] reacting as a radical then ionic hydrogen transfer agent. This strategy opened up a straightforward and efficient access to 2,3,5-trisubstituted tetrahydrofurans from readily accessible

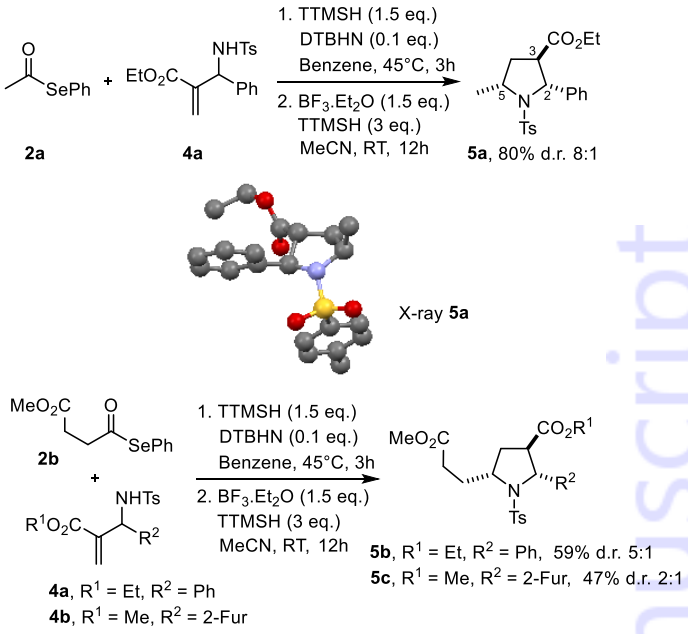
precursors. Based on this work, we describe here an extension of the methodology to the synthesis of trisubstituted pyrrolidines, showing that the simple modification of the nature of the protecting group on nitrogen (Ts, Boc, Cbz) offers additional opportunities to access various nitrogen heterocycles, including pyrrolidines **IIIa** of complementary stereochemistry, dihydropyrroles **IIIb**, but also bicyclic pyrrolizidines **IIIc** or indolizidines **IIId**. For instance, it was discovered that a Cbz-protecting group allowed the formation of the pyrrolidine **IIIa** having a *trans-trans* relative configuration, while under similar conditions, the N-Boc-analogue led to the *trans*-dihydropyrrole **IIIb** in excellent yield.



Scheme 1. Synthesis of substituted tetrahydrofurans and pyrrolidines from Baylis-Hillman adducts and selenoesters.

Results and Discussion

Preliminary experiments were carried out using N-tosyl-protected aza-Baylis-Hillman adduct **4a**, prepared from the corresponding *p*-tosylimine and ethyl acrylate.[6] Treatment of **4a** in the presence of selenoester **2a**,[4,7] as an acyl radical precursor, with TTMSH in benzene[8] and *t*-BuON=NO*t*-Bu (DTBHN) as an initiator, led to the addition product, which was not isolated, but directly submitted to an acidic treatment to trigger the cyclization into the desired iminium intermediate (Scheme 2). Addition of BF_3-OEt_2 was shown to provide the putative iminium, which was then reduced *in situ* using TTMSH as an hydride donor.[9] N-*p*-tosylpyrrolidine **5a** was thus obtained in good overall yield and satisfying diastereocontrol. Interestingly, the diastereomeric ratio estimated through ^{1}H NMR after the first step was the same at that measured on **5a**, indicating that the reduction of the iminium intermediate and generation of C2 and C5 chiral centers occurred with complete 1,3-stereocontrol, while TTMSH reduction in the first step and formation of C2 and C3 centers occurred with a 8:1 diastereocontrol. X-ray diffraction studies showed that, in good agreement with previous work in the tetrahydrofuran series,[4] **5a** possessed a 2,3,5-*trans-trans* relative configuration. The study was then extended to other N-Ts protected allylamine such as **4b** and selenoester **2b**, under similar conditions, which produced the desired N-tosylpyrrolidines **5b-c** in generally good yields, albeit with modest diastereoselectivities as compared to **5a**.



Scheme 2. Addition of acyl radical onto aza-Baylis-Hillman adducts **4a-b**.

1,2-stereocontrol during reduction of the enoyl radical, resulting from the addition of the acyl radical onto the enoate, may be rationalized invoking hydrogen-bonding between the ester C=O group and the tosylamide N-H in transition state (TS) **A**, as proposed earlier by Kündig et *al.*.[10] The bulky silicon hydride would then approach *anti* relative to the largest R^2 group to install the C2-C3-*syn* relative configuration (Figure 2). The lower diastereocontrol observed with the furyl substituent in **5c** is presently not clear, but might result from the occurrence of two energetically close TS **A** and **A'**. In the latter, a putative hydrogen bonding between the furyl oxygen and the tosylamide N-H, would lead the hydrogen to eclipse the enoyl system as in $A_{1,3}$ models, the two diastereotopic faces being weakly differentiated.[11-13] 1,3-Stereocontrol may be explained as proposed earlier in the tetrahydrofuran series.[4a] Reduction of the iminium likely proceeds through an envelope conformation such as **B** (Figure 2), with the ester group in pseudo-axial position as to maximize electrostatic effects with the iminium ions.[14] Inside approach of TTMSH on the lower energy conformer **B** thus occurs *anti* to the R^2 group to generate the 2,5-*cis* configuration.

10.1002/adsc.201700362

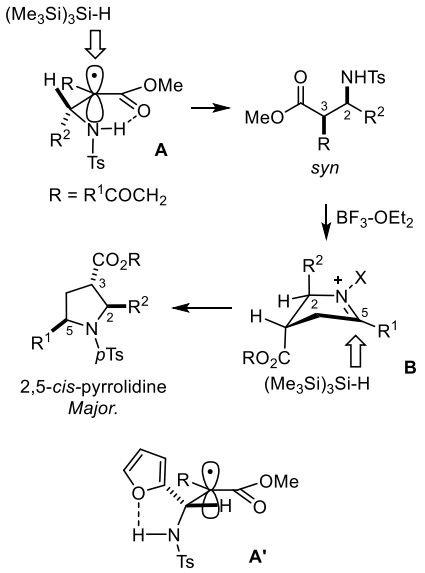
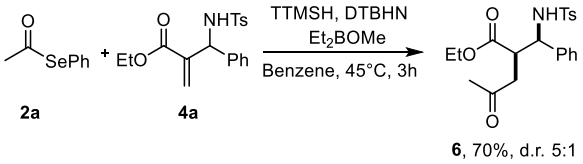


Figure 2. Rationalization of the 1,2- and 1,3-stereocontrol.

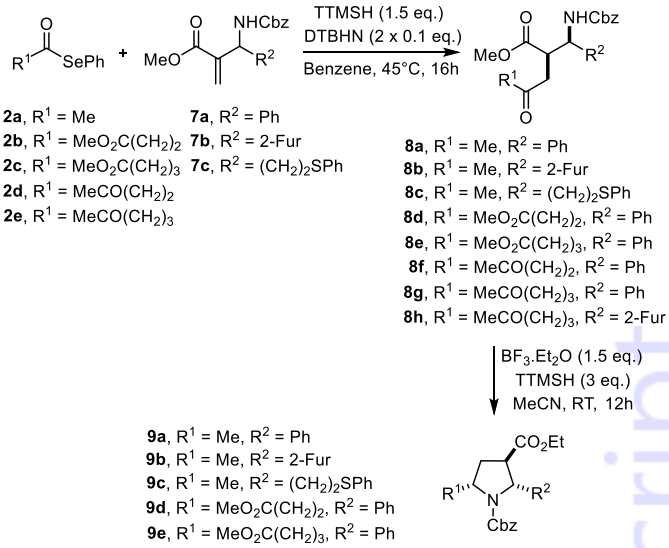
In order to improve the level of diastereocontrol during the reduction of radical intermediate **A**, the addition of **2a** onto **4a** was also attempted using Et_2BOMe to chelate the nitrogen atom and the carbonyl group (Scheme 3).[15] However, and in contrast with recent studies in the tetrahydrofuran series, the addition product **6** was obtained in good yield but with a lower stereocontrol than above (Scheme 2).



Scheme 3. Addition of acyl radical onto allylamine **4a** in the presence of Et_2BOMe as an additive.

Although this approach provided the desired pyrrolidines in good yields and satisfying sterocontrol, it was anticipated that the rather harsh N-Ts group deprotection conditions might hamper further transformation of more functionalized substrates.[16] The addition of acyl radicals was thus extended to aza-Baylis-Hillman adducts protected with the more labile, but yet stable benzyloxycarbonyl (Cbz) N-protecting group. Aza-Baylis-Hillman adducts were prepared using reported procedures[17] (see supporting information), then subjected to the radical acyl addition process, starting from various selenoesters **2a-e** (Table 1).

Table 1. Addition of acyl radical onto N-Cbz-protected aza-Baylis-Hillman adducts **7a-c**.

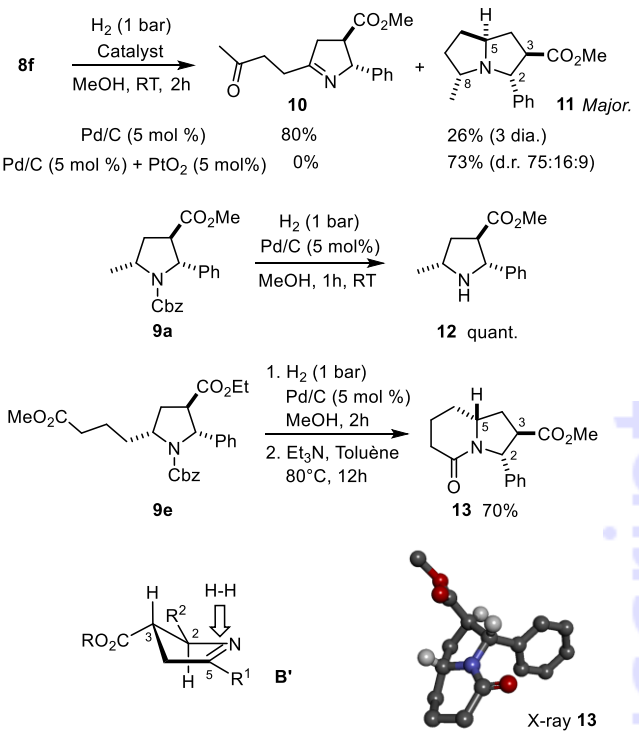


Entry	8	d.r.[a]	Yield[b]	9	d.r.[a]	Yield[b]
1	**8a**	-	-	**9a**	5:1	63[c]
2	**8b**	4:1	72	**9b**	40:34:26	34[d]
3	**8c**	3:1	70	**9c**	60:22:18	84[e]
4	**8d**	-	-	**9d**	2:1	58[c]
5	**8e**	6:1	77	**9e**	100:0	66
6	**8f**	5:1	89	-	-	-
7	**8g**	5:1	75	-	-	-
8	**8h**	4:1	60	-	-	-

[a] estimated from the ^1H NMR of the crude reaction mixture. [b] Isolated yield after chromatography. [c] Isolated yield over 2 steps (of the mixture of diastereomers). [d] Isolated yield of the major diastereomer **9b** (stereochemistry shown above). [e] Isolated yield of the inseparable mixture of the 3 diastereomers.

Using the conditions optimized in the N-Ts series, the overall sequence provided the desired N-Cbz protected pyrrolidines **9a-e** in generally good yields with moderate to excellent diastereocontrol (Table 1).[18] In certain cases, the diastereomeric acyl addition products **8** could not be separated and were directly subjected to the reduction step (Table 1, entries 1 and 4) to provide the corresponding pyrrolidines **9**. Contrasting results were however observed, depending on the nature of the R^2 substituent in **7a-c**. Reduction of the iminium was totally diastereoselective for R^2 = Ph, the d.r. of the final pyrrolidines **9a** and **9d** illustrating the stereoselectivity of the acyl radical addition (Table 1, entries 1, 4 and 5). With other R^2 groups, we observed a slightly lower diastereocontrol in both steps, as indicated by the formation of a mixture of 3 diastereomers, showing that the reduction of one iminium diastereomer was not totally stereoselective (Table 1, entries 2-3). A *trans-trans* 2,3,5-stereochemistry was proposed for the major diastereomer of **9b-c**, by analogy with that of pyrrolidine **9a**. With selenoesters **2d-e** bearing a

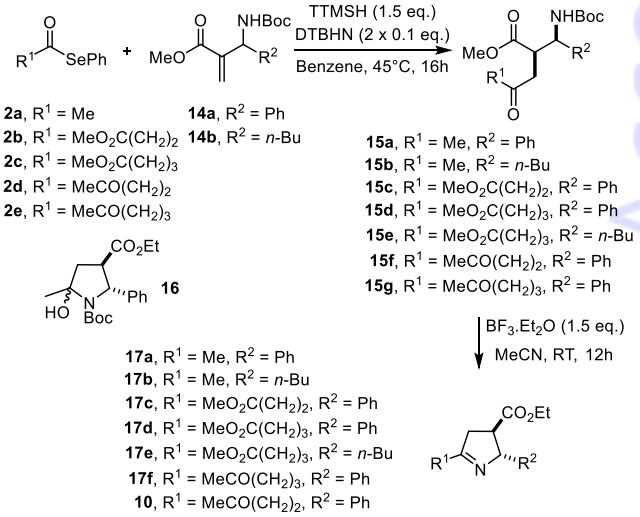
ketone functional group, the acyl addition provided the expected amino-ketones **8f-g** in excellent yield and satisfying diastereocontrol (Table 1, entries 6-7). However, all our attempts to cyclize **8f-g**, using BF_3-OEt_2 and TTMSH, failed to afford the corresponding pyrrolidines and led to starting material decomposition, in contrast with recent studies.[18] Better results were obtained through metal-catalyzed reduction (Scheme 4).[19] Hydrogenation of **8f** with 5 mol% of Pd-C thus led to dihydropyrrole **10** and pyrrolizidine **11**. The former results from the Cbz deprotection, followed by a 5-*exo* reductive amination. Further hydrogenation of the imine **10** then led to the corresponding pyrrolidine, which was not observed but directly converted, through a second reductive amination into **11** as a mixture of three separable diastereomers, the stereochemistry of the major one being assigned through 2D ^{1}H NMR (supporting information).[20] It is worth mentioning that reduction of the imine **10** through metal-catalyzed hydrogenation affords the complementary 2,5-*trans* configuration (in **11**) as compared to the 2,5-*cis* generated through TTMSH reduction (*vide infra*). In contrast with the TTMSH reduction of iminiums above (Figure 2), electrostatic effects are less important in imine metal-catalyzed hydrogenation. Therefore, an approach of H_2/Pd inside a lower energy envelope conformation such as **B'** (Scheme 4), in which both substituents at C2 and C3 are in equatorial position, is likely preferred, leading to the observed 2,5-*trans* configuration.[14d] When the reaction was repeated with PtO_2 as a catalyst,[21] only traces of **11** were observed. Finally, a combination of Pd-C and PtO_2 provided **11** in good yield again as a mixture of 3 stereoisomers, but with a satisfying diastereocontrol. Pd-C thus proved efficient to remove the N-Cbz group, while PtO_2 led to good results for the imine hydrogenation. As an illustration, pyrrolidine **9a** was converted quantitatively in only 1h into the free pyrrolidine **12** using 5 mol% of Pd-C. Similarly, treatment of pyrrolidine **9e** under the same conditions led to the indolizidinone **13** after cyclization with Et_3N. X-ray diffraction studies on **13** confirmed the 2,5-*cis* configuration obtained upon BF_3-Et_2O/TTMSH reduction. Treatment of N-Cbz pyrrolidine **9d** under the same conditions than for **9e** surprisingly did not afford the corresponding pyrrolizidinone, although Cbz-deprotection was observed on the crude reaction mixture.



Scheme 4. Cbz removal and further functionalization of pyrrolidines **9**.

Another set of experiments was performed using N-Boc protected allylamines **14a-b** and selenoesters **2a-e**. It was anticipated that the lability of the Boc group under acidic conditions would allow an easy formation of the iminium intermediate after acyl radical additions and N-Boc deprotection with Brønsted or Lewis acids.[22] Reduction *in situ* of the so-formed iminium with TTMSH would thus provide the deprotected pyrrolidines in a two steps one-pot process.

Table 2. Addition of acyl radical onto N-Boc-protected allylamines **14a-b**.

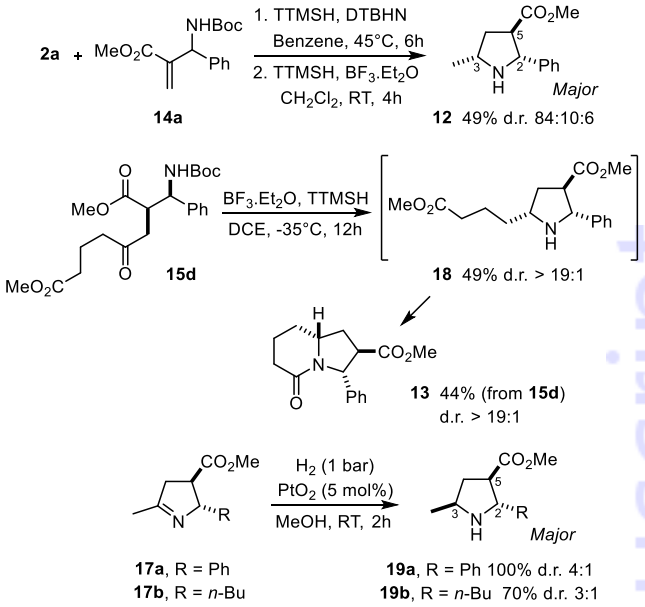


10.1002/adsc.201700362

Entry	15	d.r.[a)]	Yield[b)]	Imine	d.r.[a)]	Yield[b)]
1	**15a**	10:1	68[c)]	**17a**	10:1	70
2	**15b**	-	-	**17b**	3:1	56
3	**15c**	-	-	**17c**	10:1	66
4	**15d**	10:1	84	**17d**	10:1	69
5	**15e**	-	-	**17e**	3.5:1	61
6	**15f**	-	-	**10**	6:1	60
7	**15g**	6:1	79	**17f**	6:1	75[d)]

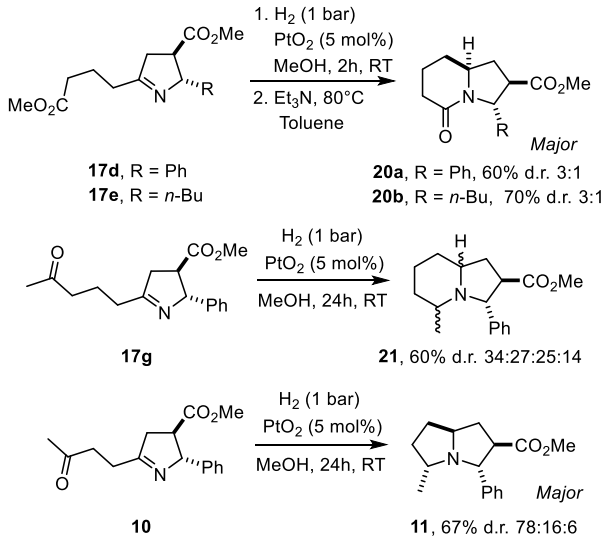
[a)] estimated from the ^{1}H NMR of the crude reaction mixture. [b)] Isolated yield after chromatography. [c)] 14% of hemiaminal **16** was also isolated. [d)] 56% overall yield over 2 steps from **15g**.

Preliminary experiments with aza-Baylis-Hillman adduct **14a** and selenoester **2a** led, as expected, to the addition product **15a** with a good diastereocontrol, along with the corresponding hemiaminal **16** (Table 2, entry 1). Direct treatment of the crude reaction mixture containing **15a** with BF_3-OEt_2 and TTMSH led to the N-Boc deprotection and formation of the imine **17a** with a 10:1 diastereomeric ratio, indicating that **16** had the same relative configuration and was issued from the cyclization of **15a**. The formation of **17a** as a unique product also showed that the silane was unable to reduce the imine under these Lewis-acid conditions. Treatment of **15a** with BF_3-OEt_2 alone effectively led to **17a** in 70% yield and 10:1 d.r. (Table 1, entry 1). When the two-steps reaction was repeated with allylamine **14b**, bearing an alkyl substituent in allylic position, imine **17b** was obtained with a lower diastereocontrol (entry 2), in good agreement with previous observations made with N-Ts and N-Cbz analogues (see for instance **8c**, Table 1). This general trend was followed, whatever the nature of the selenoester **2**, as shown by the diastereocontrol observed during the formation of imines **10** and **17c-f** (Table 1, compare entries 3-4 and 6-7 with entry 5).
The failure during reduction of imine **17a** with TTMSH in the presence of BF_3-OEt_2 was attributed to the presence of CH_3CN as a solvent, which coordinates to the Lewis acid, thus preventing the formation of the iminium intermediate. When the reaction was performed in CH_2Cl_2 instead, the iminium generated *in situ* from **2a** and **14a** was effectively reduced by TTMSH, affording **12** (Scheme 5), in modest yield but satisfying diastereocontrol, with spectroscopic data matching those of the pyrrolidine prepared from **9a** (Scheme 4). Better diastereocontrol was observed when carrying out the reduction of **15d** in DCE at low temperature. Pyrrolidine **18** was obtained with high diastereocontrol, although with modest conversion (30% of imine **17d** was also isolated), and slowly cyclized into indolizidinone **13**, identical to that prepared from N-Cbz pyrrolidine **9e** (Scheme 4). Interestingly, when imines **17a-b** were hydrogenated using PtO_2 as a catalyst, pyrrolidines **19a-b** having the complementary 2,3,5-*trans-cis* relative configuration were formed in good yield, albeit with modest diastereocontrol.[19,21] Comparison between ^{1}H NMR of the crude mixture of both reactions, revealed that the major diastereomer in **19a** was the minor isomer (6%) in **12**.



Scheme 5. Reduction of imines with TTMSH and H_2-PtO_2.

Imines **17d** and **17e** were also hydrogenated using PtO_2 as a catalyst, affording indolizidinones **20a-b** having the complementary stereochemistry to that of **13** above (Scheme 6). This procedure was also extended to imines **17g** and **10** having an additional ketone functional group. Under these conditions, **17g** led to the corresponding indolizidine **21** as a mixture of 4 stereoisomers in a 60% combined yield. Finally, more encouraging results were obtained with imine **10**, which under similar conditions, led to pyrrolizidine **11** identical to that prepared from **8f** and with a satisfying stereocontrol (Scheme 4). Compounds such as **11**, having 4 stereocenters, may thus be prepared in good yield and reasonable diastereocontrol in only 4 steps and two-pot from simple starting materials.



Scheme 6. Formation of pyrrolizidines and indolizidines from imines **17d-g** and **10**.

Conclusion

In summary, we reported here the stereocontrolled access to N-protected and unprotected pyrrolidines having stereocenters at 2-, 3- and 5-positions in good overall yields and high diastereocontrol. The level of stereocontrol was shown to be highly dependent on the nature of the substituent on the stereocenter of the starting aza-Baylis-Hillman adducts. Varying the nature of the protecting group on nitrogen also allowed further transformations. For instance, acyl addition products having N-Cbz groups could be cyclized stereoselectively into the Cbz-protected pyrrolidines. In contrast, the analogous N-Boc adducts were unprotected under Lewis-acidic conditions, leading after cyclization to the corresponding stable dihydropyrroles. Pt-catalyzed hydrogenation of the latter gave access to pyrrolidines having a relative configuration, complementary to that of pyrrolidines obtained through the BF_3-OEt_2/$(Me_3Si)_3SiH$ method. This strategy finally offers a rapid entry toward indolizidinones and pyrrolizidines with up to 4 stereocenters in only 4 steps and two-pot from readily available selenoesters and aza-Baylis-Hillman adducts.

Experimental Section

General procedure for the synthesis of pyrrolidines 5 and 9: To a mixture of phenyl selenoester (1.2 eq.), N-Ts or N-Cbz *aza*-Baylis-Hillman adduct (1 eq.) and TTMSH (1.5 eq.) in benzene (0.1 M) was added DTBHN (0.1 eq.). The reaction mixture was heated at 45°C and stirred for 4h. DTBHN was added (0.1 eq.) and the reaction mixture was stirred for an additional 12h at this temperature. The reaction mixture was concentrated under reduced pressure and the crude was dissolved in MeCN (0.1 M). TTMSH (3 eq.) was added followed by BF_3-OEt_2 (1.5 eq.). The reaction mixture was stirred at 25°C for 12h and quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted twice with EtOAc and combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by chromatography.

General procedure for the synthesis of dihydropyrroles 17: To a mixture of phenyl selenoester (1.2 eq.), N-Boc *aza*- Baylis-Hillman adduct (1 eq.) and TTMSH (1.5 eq.) in benzene (0.1 M) was added DTBHN (0.1 eq.). The reaction mixture was heated at 45°C and stirred for 4h. DTBHN was added (0.1 eq.) and the reaction mixture was stirred for an additional 12h at this temperature. The reaction mixture was concentrated under reduced pressure and the crude was dissolved in MeCN (0.1 M). $BF_3.OEt_2$ (2 eq.) was added and the reaction mixture was stirred at 25°C for 12h and quenched by addition of a saturated solution of $NaHCO_3$. The aqueous layer was extracted twice with EtOAc and combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by chromatography.

Experimental Details

Crystal Structures CCDC1531874 (**5a**), CCDC 1531876 (**13**) 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

SG thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a PhD fellowship. The Agence Nationale de la Recherche (ANR) (Spirosyn, N° 11-BS07-006-02) and CNRS are gratefully acknowledged for financial support.

References

[1] a) R. A. Saporito, M. A. Donnelly, R. A. Norton, H. M. Garraffo, T. F. Spande, J. W. Daly, *Proc. Natl. Acad. Sci.* **2007**, *104*, 8885; b) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556; c) F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213; d) J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773; e) J. Robertson, K. Stevens, *Nat. Prod. Rep.* **2014**, *31*, 1721; f) J. W. Daly, *Proc. Natl. Acad. Sci.* **1995**, *92*, 9; g) J. Diaz Gonzalo, *Toxins* (Basel) **2015**, *7*, 5408; h) J. R. Liddell, *Nat. Prod. Rep.* **1998**, *15*, 363; i) V. Naithani, S. Haider, P. Kakkar, *J. Ecophysiol. Occup. Health* **2001**, *1*, 339. j) R. E. Schwartz, J. Liesch, O. Hensens, L. Zitano, S. Honeycutt, G. Garrity, R. A. Fromtling, J. Onishi, R. Monaghan, *J. Antibiot.***1988**, *41*, 1774.

[2] a) S. Gerber-Lemaire, L. Juillerat-Jeanneret, *Chimia* **2010**, *64*, 634; b) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139; c) A. El Nemr,

Tetrahedron **2000**, *56*, 8579; d) T. Ayad, Y. Genisson, M. Baltas, *Curr. Org. Chem.* **2004**, *8*, 1211.

[3] a) J. Royer, *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley: Weinheim, 2009; b) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Eur. J.* **2009**, *15*, 7808; c) G. Broggini, G. Zecchi, *Synthesis* **1999**, 905; d) A. Goti, S. Cicchi, F. M. Cordero, V. Fedi, A. Brandi, *Molecules* **1999**, *4*, 1; e) W. S. Lee, K. C. Jang, J. H. Kim, K. H. Park, *Chem. Commun.* **1999**, 251; f) Z. Shao, J. Chen, Y. Tu, L. Li, H. Zhang, *Chem. Commun.* **2003**, 1918; g) Y. K. Kim, T. Livinghouse, *Angew. Chem., Int. Ed.* **2002**, *41*, 3645; *Angew. Chem.* **2002**, *114*, 4344; h) S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem., Int. Ed.* **2002**, *41*, 164; *Angew. Chem.* **2002**, *114*, 172; i) J.-S. Ryu, T. J. Marks, F. E. McDonald, *Org. Lett.* **2001**, *3*, 3091; j) C. Bhat, S. G. Tilve, *RSC Adv.* **2014**, *4*, 5405; k) S. G. Pyne, A. S. Davis, N. J. Gates, J. P. Hartley, K. B. Lindsay, T. Machan, M. Tang, *Synlett* **2004**, 2670; l) J. Robertson, M. A. Peplow, J. Pillai, *Tetrahedron Lett.* **1996**, 5825; m) R. V. Stevens, *Acc. Chem. Res.* **1977**, *10*, 193; n) H. Yoda, *Curr. Org. Chem.* **2002**, *6*, 223; o) G. Lapointe, K. Schenk, P. Renaud, *Chem. Eur. J.* **2011**, *17*, 3207; p) D. J. Hart, *Radical Cyclizations in Alkaloid Synthesis* in *Radicals in Organic Synthesis*, Ed. P. Renaud M. P. Sibi, Wiley-VCH, Verlag GmbH, 2001, Vol. 2, 279.

[4] a) S. Grélaud, V. Desvergnes, Y. Landais, *Org. Lett.* **2016**, *18*, 1542; b) S. Grélaud, J. Lusseau, Y. Landais, *Eur. J. Org. Chem.* **2017**, 1323.

[5] a) C. Chatgilialoglu, *Chem. Eur. J.* **2008**, *14*, 2310 and references therein; b) C. Chatgilialoglu, J. Lalevée, *Molecules* **2012**, *17*, 527; c) C. Chatgilialoglu, *Acc. Chem. Res.* **1992**, *25*, 188.

[6] For a reviews on Aza-Baylis-Hillman reaction, see: a) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1; b) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, *Curr. Org. Chem.* **2005**, *9*, 1315; c) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811. For selected examples, see: d) P. Perlmutter, C. C. Teo, *Tetrahedron Lett*. **1984**, *25*, 5951; e) T. Yukawa, B. Seelig, Y. Xu, H. Morimoto, Y. Xu, H. Morimoto, S. Matsunaga, A. Berkessel, M. Shibasaki, *J. Am. Chem. Soc.*, **2010**, *132*, 11988; f) M. Shi, G.-N. Ma, J. Gao, *J. Org. Chem.*, **2007**, *72*, 9779; g) K. Matsui, S. Takizawa, H. Sasai, *Synlett*, **2006**, 761. For selected reports on the reactivity of aza-Baylis-Hillman adducts, see: h) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; i) S.-e. Syu, Y.-T. Lee, Y.-J. Jang, W. Lin, *J. Org. Chem.*, **2011**, *76*, 2888.

[7] D. L. Boger, R. J. Mathvink, *J. Org. Chem.* **1992**, *57*, 1429.

[8] 1,2-Dichloroethane (DCE) may also be used instead of benzene leading to similar diastereocontrol, but generally lower yields.

[9] TTMSH was consistently used throughout this study, as we observed earlier in the tetrahydrofuran series[4a,b] that it generally provides higher diastereocontrol than cheaper Et_3SiH.

[10] E. P. Kündig, L.-H. Xu, P. Romanens, *Tetrahedron Lett.* **1995**, *36*, 4047.

[11] For radical addition of alkyl radicals to Baylis-Hillman adducts, see: a) M. Bulliard, H.-G. Zeitz, B. Giese, *Synlett* **1991**, 423; b) B. Giese, M. Bulliard, J. Dickhaut, R. Halbach, C. Hassler, U. Hoffmann, B. Hinzen, M. Senn, *Synlett* **1995**, 116. For addition of acyl radicals to enoates, see: c) F. A. Macias, J. M. G. Molinillo, G. M. Massanet, F. Rodriguez-Luis, *Tetrahedron* **1992**, *48*, 3345; d) S. Esposti, D. Dondi, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed.* **2007**, *46*, 2531; *Angew. Chem.* **2007**, *119* 2583.

[12] For reviews, see: a) D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions;* VCH: Weinheim, 1995; b) N. A. Porter, B. Giese, D. P. Curran, *Acc. Chem. Res.* **1991**, *24*, 296; c) D. J. Hart, R. Krishnamurthy, *Synlett* **1991**, 412; d) D. P. Curran, P. S. Ramamoorthy, *Tetrahedron* **1993**, *49*, 4841; e) B. Guérin, W. W. Ogilvie, Y. Guindon, in *Radicals in Organic Synthesis*; Eds P. Renaud, M. P. Sibi, VCH: Weinheim, 2001; Vol. 1, 441.

[13] I. Chataigner, C. Panel, H. Gérard, S. R. Piettre, *Chem. Commun.* **2007**, *31*, 3288.

[14] a) A. Schmitt, H.-U. Reissig, *Synlett* **1990**, 40; b) C. Brückner, H. Holzinger, H.-U. Reissig, *J. Org. Chem.* **1988**, *53*, 2450; c) H.-U. Reissig, H. Holzinger, G. Glomsda, *Tetrahedron* **1989**, *45*, 3139; d) C. H. Larsen, B. H. Ridgway, J. T. Shaw, D. M. Smith, K. A. Woerpel, *J. Am. Chem. Soc.* **2005**, *127*, 10879; e) E. R. van Rijssel, P. van Delft, G. Lodder, H. S. Overkleeft, G. A. van der Marel, D. V. Filippov, J. D. C. Codée, *Angew. Chem. Int. Ed.* **2014**, *53*, 10381; *Angew. Chem.* **2014**, *126*, 10549.

[15] a) H. Urabe, K. Yamashita, K. Suzuki, K. Kobayashi, F. Sato, *J. Org. Chem.* **1995**, *60*, 3576; b) Y. Guindon, J. Rancourt, *J. Org. Chem.* **1998**, *63*, 6554; c) N. Mase, S. Wake, Y. Watanabe, T. Toru, *Tetrahedron Lett.* **1998**, *39*, 5553; d) N. Mase, Y. Watanabe, T. Toru, *Tetrahedron Lett.* **1999**, *40*, 2797; e) I. Denissova, L. Maretti, B. C. Wilkes, J. C. Scaiano, Y. Guindon, *J. Org. Chem.* **2009**, *74*, 2438; f) J.-F. Brazeau, A.-A. Guilbault, J. Kochuparampil, P. Mochirian, Y. Guindon, *Org. Lett.* **2010**, *12*, 36.

[16] P. G. M. Wuts, T. W. Greene *in Greene's Protective Groups in Organic Synthesis*, Wiley Interscience, J. Wiley & Sons, Inc., Hoboken, 2007, 4th Ed., p 855. The NTs group may for instance be unprotected using single electron reduction with Mg in MeOH, see: L. C. Pattenden, H. Adams, S. A. Smith, J. P. A. Harrity, *Tetrahedron* **2008**, *64*, 2951.

[17] C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.* **2009**, *48*, 5694; *Angew. Chem.* **2009**, *121*, 5804.

[18] a) N. Toyooka, D. Zhou, H. Nemoto, *J. Org. Chem.* **2008**, *73*, 4575; b) N. Toyooka, D. Zhou, H. Nemoto, Y. Tezuka, S. Kadota, N. R. Andriamaharavo, H. M. Garraffo, T. F. Spande, J. W. Daly, *J. Org. Chem.* **2009**, *74*, 6784; c) F. Abels, C. Lindemann, E. Koch, C. Schneider, *Org. Lett.* **2012**, *14*, 5972; d) F. Abels, C. Lindemann, C. Schneider, *Chem. Eur. J.* **2014**, *20*, 1964.

[19] a) G. V. Thanh, J. P. Célérier, A. Fleurant, C. Grandjean, S. Rosset, G. Lhommet, *Heterocycles* **1996**, *43*, 1381; b) A. López-Pérez, J. Adrio, J. C.

10.1002/adsc.201700362

Carretero, *Angew. Chem. Int. Ed.* **2009**, *48*, 340; *Angew. Chem.* **2009**, *121*, 346.
[20] The configuration of the other two stereoisomers could not be determined with certainty through ^{1}H NMR.
[21] a) D. Giomi, R. Alfini, A. Micoli, E. Calamai, C. Faggi, A. Brandi, *J. Org. Chem.* **2011**, *76*, 9536; b) V. Liautard, D. Jardel, C. Davies, M. Berlande, T. Buffeteau, D. Cavagnat, F. Robert, J.-M. Vincent, Y. Landais, *Chem. Eur. J.* **2013**, *19*, 14532.
[22] C. Agami, F. Couty, *Tetrahedron* **2002**, *58*, 2701.

10.1002/adsc.201700362

FULL PAPER

Acyl radical Addition onto aza-Baylis-Hillman Adducts. A Stereocontrolled access to 2,3,5-Trisubstituted Pyrrolidines

Adv. Synth. Catal. **2017**, *Volume*, Page – Page

Simon Grélaud, Jonathan Lusseau, Stéphane Massip, and Yannick Landais*