ORGANIC LETTERS

2011
Vol. 13, No. 12
3000–3003

Diastereoselective Intramolecular Friedel–Crafts Alkylation of Tetralins

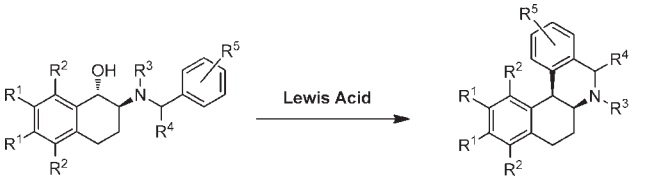
Clémence Liébert,[†] Marion K. Brinks,[†] Andrew G. Capacci,[†] Matthew J. Fleming,[‡] and Mark Lautens*,[†]

Davenport Chemical Laboratories, Department of Chemistry, University of Toronto, 80 St George Street, Toronto, Ontario M5S 3H6, Canada, and Chemical Development and Catalysis Department, Solvias AG, Roemerpark 2, 4303 Kaiseraugst, Switzerland

mlautens@chem.utoronto.ca

Received March 29, 2011

ABSTRACT



An efficient and versatile synthesis of *cis*-hexahydrobenzophenanthridines starting from readily available tetralins has been developed using an intramolecular Friedel–Crafts alkylation as a key step. The substrates were prepared via a highly stereocontrolled rhodium-catalyzed ring-opening reaction of *meso*-oxabicyclic alkenes and a hydrogenation sequence. Thus, a wide variety of complex tetracyclic compounds have been isolated with a high level of regio-, diastereo-, and enantioselectivity.

Advanced studies have been recently reported in the field of benzylic arylation using a Friedel–Crafts (FC) alkylation protocol. These newly developed methodologies allowed the use of milder reaction conditions and inexpensive and relatively nontoxic catalysts.[1] Within this area, there is a growing interest in the utilization of π-activated alcohols as a replacement of the less widely available and more toxic organo halides.[2] Additionally, Bach and co-workers made significant progress in the domain of diastereoselective FC alkylations.[3,4] More recently, our group disclosed an FC process for the intermolecular *trans*-selective benzylic arylation of tetralin systems.[5] We next focused our attention on the case of the intramolecular FC alkylation of tetralins so as to efficiently and stereoselectively access more complex hexahydrobenzophenanthridines. Such fused tetracyclic

[†] University of Toronto.
[‡] Solvias AG.

(1) (a) Zhang, X.; Rao, W.; Wai Hong Chan, S.; P. *Org. Biomol. Chem.* **2009**, *7*, 4186. (b) Deng, X.; Liang, J. T.; Liu, J.; McAllister, H.; Schubert, C.; Mani, N. S. *Org. Process Res. Dev.* **2007**, *11*, 1043. (c) Hashmi, A. S. K.; Schwarz, L.; Rubenbauer, P.; Blanco, M. C. *Adv. Synth. Catal.* **2006**, *348*, 705. (d) Liu, J.; Muth, E.; Flçrke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, G. *Adv. Synth. Catal.* **2006**, *348*, 456. (e) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033. (f) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691. (g) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (h) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238.

(2) (a) Emer, E; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentis, F.; Cozzi, P. *Eur. J. Org. Chem.* **2011**, *4*, 647. (b) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (c) Muzart, J. *Tetrahedron* **2008**, *64*, 5815.

(3) (a) Stadler, D.; Bach, T. *J. Org. Chem.* **2009**, *74*, 4747. (b) Stadler, D.; Goeppert, A.; Rasul, G.; Olah, G. A.; Surya Prakash, G. K.; Bach, T. *J. Org. Chem.* **2009**, *74*, 312. (c) Stadler, D.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557. (d) Stadler, D.; Bach, T. *Chem. Asian J.* **2008**, *3*, 272. (e) Rubenbauer, P.; Bach, T. *Adv. Synth. Catal.* **2008**, *350*, 1125. (f) Stadler, D.; Mühlthau, F.; Rubenbauer, P.; Herdtweek, E.; Bach, T. *Synlett* **2006**, 2573. (g) Mühlthau, F.; Stadler, D.; Goeppert, A.; Olah, G. A.; Surya Prakash, G. K.; Bach, T. *J. Am. Chem. Soc.* **2006**, *128*, 9668. (h) Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* **2005**, *127*, 9348.

(4) (a) Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008**, *10*, 3037. (b) Enders, D.; Del Signore, G.; Berner, O. M. *Chirality* **2003**, *15*, 510.

(5) Davoust, M.; Kitching, J. A.; Fleming, M. J.; Lautens, M. *Chem.—Eur. J.* **2010**, *17*, 50.

(6) (a) Michaelides, M. R.; Hong, Y. *(Abbot Laboratories)*, US5597832 A, 1997. (b) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. (c) Lovenberg, T. W.; Brewster, W. K.; Mottola, D. M.; Lee, R. C.; Riggs, R. M.; Nichols, D. E.; Lewis, M. H.; Mailman, R. B. *Eur. J. Pharmacol.* **1989**, *166*, 111.

10.1021/ol2008236
Published on Web 05/18/2011

skeletons are often found in pharmaceutically relevant target molecules (Figure 1).[6] Therefore, the development of a versatile and selective method to synthesize highly substituted hexahydrobenzophenanthridines is warranted.

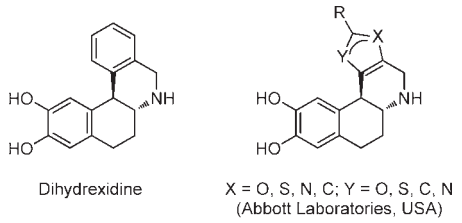
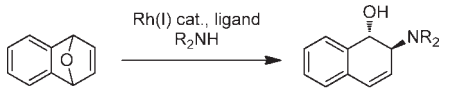


Figure 1. Pharmaceutically active compounds used in the treatment of psychiatric and neurological disorders.

In 2000, our group reported the rhodium(I)-catalyzed asymmetric ring-opening (ARO) of *meso*-oxabicyclic alkenes **1** (Scheme 1).[7,8] Thus, a wide variety of *trans*-tetralins **2** were readily prepared with a high level of regio- and diastereoselectivity (>99:1) using numerous amine nucleophiles. Excellent ee's (up to 99% ee) were also achieved when the achiral ligand DPPF was replaced by the Josiphos-type ligand PPF-P^{t}Bu$_2$. Subsequent hydrogenation of these tetralins **2** delivered the required substrates for the intramolecular FC alkylation study.[9]

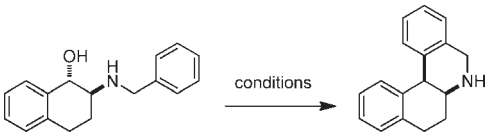
Scheme 1. Rh(I)-Catalyzed ARO of *meso*-Oxabicycles



1 2

We first investigated the conversion of the racemic tetralin **3** into the hexahydrobenzophenanthridine **4** (Table 1). Although $AlCl_3$ was the best Lewis acid (LA) to undergo the intermolecular FC alkylation when stirred in dichloromethane (DCM),[5] in the case of the intramolecular substrate **3**, only moderate yields were achieved (Table 1, entries 1 and 2). Performing the reaction in nitromethane ($MeNO_2$) instead of DCM gave similar results (Table 1, entries 3 and 4). Interestingly, the use of iron(III) as LA, previously reported by Beller and coworkers,[1h] showed the best results. Indeed, treatment of tetralin **3** with 2 equiv of $FeCl_3 \cdot 6H_2O$ in DCM at 60 °C for 24 h provided the desired product in 95% yield (Table 1, entry 5). Pure *cis*-hexahydrobenzophenanthridine **4** was obtained without further purification, and its relative stereochemistry at the ring junction was confirmed by NMR ^{1}H NOE experiments. Finally, diminishing the number of equivalents of LA only led to the recovery of the starting material (Table 1, entry 8). Coordination of the LA with the amine and/or with the eliminated water might consume the LA, making the use of an extra equivalent of LA necessary.

Table 1. Optimization Studies



3 4

entry	Lewis acid	equiv	solvent	temp (°C)	yield[a] (%)
1[b]	$AlCl_3$	2	DCM	rt	45
2	$AlCl_3$	2	DCM	60	56
3	$AlCl_3$	2	$MeNO_2$	rt	32
4	$AlCl_3$	2	$MeNO_2$	60	54
5[c]	$FeCl_3 \cdot 6H_2O$	2	DCM	60	95
6[d]	$FeCl_3 \cdot 6H_2O$	2	$MeNO_2$	60	0
7[d]	$FeCl_3 \cdot 6H_2O$	2	dioxane	60	0
8[d]	$FeCl_3 \cdot 6H_2O$	1	DCM	60	0

[a] Yield of pure product obtained after column chromatography and stirring the reaction for 24 h. [b] Reaction stirred only for 4 h. [c] Crude yield, no purification needed. [d] No conversion, only starting material recovered.

With these results in hand, we next explored the scope of the reaction, varying first the substituents on the aromatic ring of the tetralin (Table 2). Of primary importance, all *cis*-hexahydrobenzophenanthridines **6**–**12** were prepared with a high level of diastereo- and enantioselectivity regardless of the steric and/or electronic effects (Table 2, entries 1–4). Furthermore, no loss of ee was observed after both hydrogenation and FC alkylation steps. The lower yield observed in the case of the dimethoxytetralin **7** can be explained by the higher reactivity of the substrate, thus leading to the formation of side-products under the standard reaction conditions (Table 2, entry 2).[10] Noteworthy is that the difluorotetralin **9** was readily converted into the desired *cis*-hexahydrobenzophenanthridine **10** (Table 2, entry 3). Another interesting result is the fully substituted

(7) (a) Fleming, M. J.; Lautens, M. *Carbon–Heteroatom Bond Formation by Rh(I)-Catalyzed Ring-Opening Reactions in Catalyzed Carbon–Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley: New York, 2011; pp 411–436. (b) Webster, R.; Boyer, A.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418. (c) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. (e) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043. (f) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (g) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650.

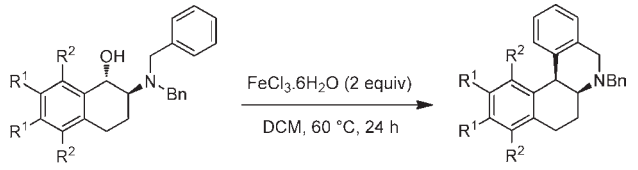
(8) For a review, see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(9) It was mandatory to remove the double bond prior to the FC alkylation since the tetralin could easily aromatize in the presence of an acid source.

(10) In this case, the major side product observed was the enamine, corresponding to the elimination of the alcohol functionality.

cis-hexahydrobenzophenanthridine **12** which was isolated in 79% yield and 98% ee (Table 2, entry 4).

Table 2. Scope of the Reaction Varying R^1 and R^2 Groups

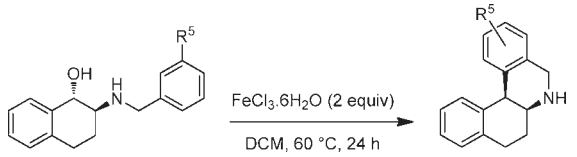


entry	substrate	R^1, R^2	product	yield[a] (%), ee (%)
1[b]	**5**	H, H	**6**	99, 98
2[c]	**7**	OMe, H	**8**	59, 92
3	**9**	F, H	**10**	88, 98
4	**11**	Br, Me	**12**	79, 98

[a] Yield of pure product after column chromatography. [b] Crude yield, no purification needed. [c] $AlCl_3$ was used as LA.

Substrates bearing substituents on the *meta*-position of the reacting aryl were then investigated (Table 3). While the desired methyl- and chloro-substituted products **14** and **16** were prepared in good yields and excellent regioselectivities (Table 3, entries 1 and 2), the less sterically hindered fluoro- and methoxyhexahydrobenzophenanthridines **18** and **20** were generated in 96% and 91% yields but as *para*:*ortho* mixtures (85:15 and 72:18, respectively, Table 3, entries 3 and 4). It is important to mention that the lower ee observed in the case of product **16** resulted from the reduced ee we obtained at the Rh(I)-catalyzed ARO reaction using the less nucleophilic primary amines as coupling partners.

Table 3. Scope of the Reaction with Varying R^5 Group

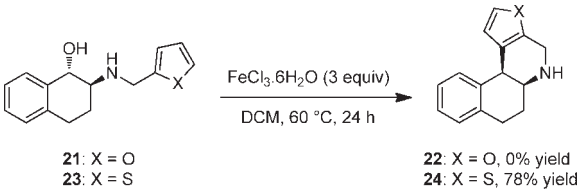


entry	substrate	R^5	product	yield[a] (%), rs (*p*:*o*),[b], ee (%)
1[c,d]	**13**	Me	**14**	99 (>95:5)
2	**15**	Cl	**16**	88 (>95:5), 74
3[c,d]	**17**	F	**18**	96 (85:15)
4[d]	**19**	OMe	**20**	91 (72:28)

[a] Yield of pure product after column chromatography. [b] Regioselectivity (rs) *para*:*ortho* relative to the new C–C bond formed. [c] Crude yield, no purification needed. [d] No ee determined as no suitable conditions could be found to achieve a desired peaks separation.

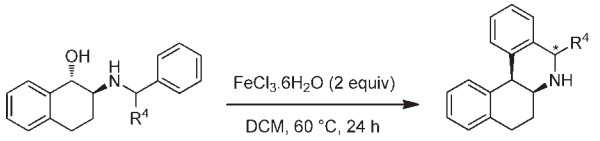
In addition, the use of heteroaryls was examined (Scheme 2). Though the thiophene substrate **23** was easily transformed into the desired *cis*-product **24** in 78% yield,[11] only decomposition was observed in the case of the furan **21**.

Scheme 2. Intramolecular FC Alkylation with Heteroaryls



To further expand the scope of the reaction, substitution at the benzylic position was investigated (Table 4). To this end, racemic branched amines were used for the Rh(I)-catalyzed ARO reaction, leading to the formation of diastereoisomeric mixtures. The diastereoisomers were separately subjected to the hydrogenation step to give compounds **(*S*)-25** and **(*R*)-25** which were readily converted into the corresponding *cis*-hexahydrobenzophenanthridines (Table 4, entries 1 and 2). Treatment of compound **(*R*)-27** with R^4 being an ethyl delivered the desired product **(*R*)-28** in 83% yield (Table 4, entry 3). To our delight, the reaction proceeded with diastereotopic face differentiation, as *cis*-hexahydrobenzophenanthridine **(*R*)-30** was produced as a single diastereoisomer starting from substrate **29** (Table 4, entry 5).[12]

Table 4. Scope of the Reaction with Varying R^4 Group



entry	substrate	R^4	product	yield[a] (%), ee (%)
1[b,c]	**(*S*)-25**	Me	**(S)-26**	99
2	**(*R*)-25**	Me	**(R)-26**	91, 76
3[c]	**(*R*)-27**	Et	**(*R*)-28**	83
4	**29**	Ph	**(*R*)-30**	85, 78

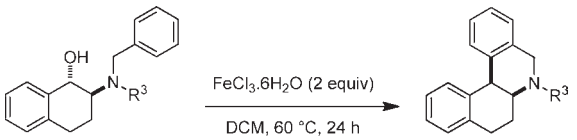
[a] Yield of pure product after column chromatography. [b] Crude yield, no purification needed. [c] No ee determined as no suitable conditions could be found to achieve a desired peaks separation.

Interestingly, the presence of suitable protecting groups for the amine functionality was also tolerated under the reaction conditions (Table 5). Amines protected by a methyl, an acetate, or a tosyl group delivered the desired products **32**–**36** in yields up to 99% (Table 5, entries 1–3). However, when a Boc or a Cbz group was used, no formation of the desired *cis*-hexahydrobenzophenanthridines **38** and **40** was observed (Table 5, entries 5 and 6). Instead, carbamate **41** was repeatedly isolated in high yields (Figure 2).

(11) No ee could be determined as no suitable conditions could be found to achieve a desired peak separation.

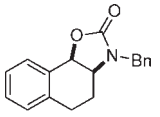
(12) The stereochemistry of compounds **(*S*)-26**, **(*R*)-26**, **(*R*)-28**, and **(*R*)-30** was confirmed by NMR ^{1}H NOE experiments.

Table 5. Scope of the Reaction with Varying R^3 Group



entry	substrate	R^3	product	yield[a] (%)
1	**31**	Me	**32**	99
2[b]	**33**	Ac	**34**	78
3	**35**	Ts	**36**	49
4[c,d]	**37**	Boc	**38**	0
5[d]	**39**	Cbz	**40**	0

[a] Yield of pure product after column chromatography. [b] Alcohol functionality was also protected by an acetate group. [c] Reaction stirred at rt. [d] Corresponding side product **41** was isolated in 94% yield (see Figure 1).



41

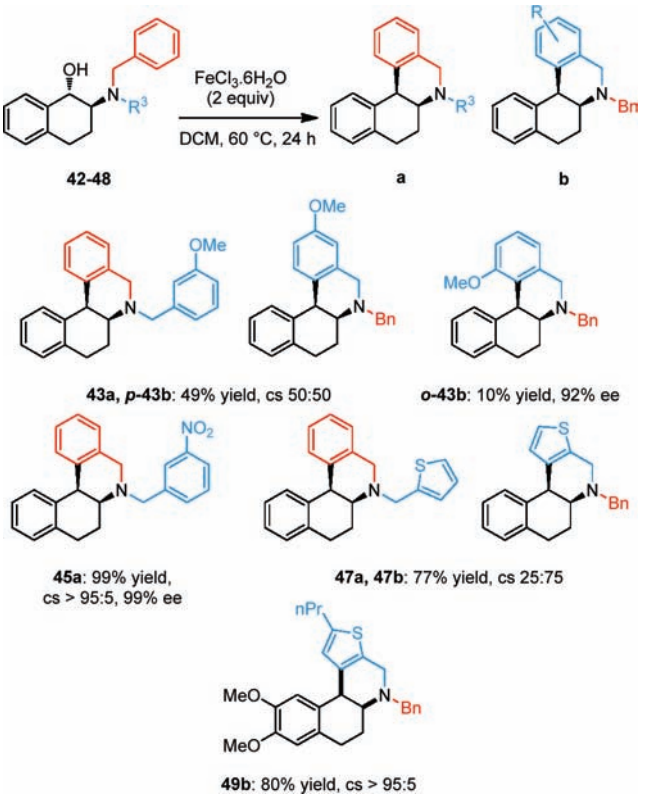
Figure 2. Isolated side product starting from Boc- and Cbz-protected amines.

Finally, we examined the chemoselectivity of the reaction (Scheme 3). Substrates presenting two different aryl groups were synthesized. While perfect chemoselectivity was obtained in the case of the electron-poor substrate **44** (the neutral phenyl ring being the only one reacting), formation of a complex mixture was observed for the electron-rich substrate **42** (Scheme 3, product **45a** vs products **43a**, ***p*-43b**, and ***o*-43b**). In addition, moderate chemoselectivity was achieved when one phenyl ring was replaced by a thiophene.[13] However, introducing a *n*-propyl group at 4-position of the thiophene drastically enhanced the chemoselectivity of the reaction as compound **49b** was isolated as a single isomer in 80% yield.[14]

Initial mechanistic studies suggested that the reaction could proceed via the formation of a stabilized intermediate carbocation species. Indeed, treatment of both ***syn*-48** and ***anti*-48** compounds in the presence of $FeCl_3 \cdot 6H_2O$ furnished the same *cis*-product **49b**.[15] Further investigations to probe the mechanism of the reaction are currently underway.

In conclusion, we have developed a new and efficient route to substituted *cis*-hexahydrobenzophenanthridines starting from tetralin systems. The initial Rh(I)-catalyzed ARO step establishes the regiochemistry and the relative

Scheme 3. Chemoselectivity of the Reaction



and absolute stereochemistry of the tetralins. Subsequent FC alkylation of the hydrogenated tetralins delivers the desired *cis*-hexahydrobenzophenanthridines in high yields and diastereoselectivities. Of primary importance, no loss of enantioselectivity is observed under the reaction conditions. Thus, numerous tetracyclic products presenting various substitution patterns have been prepared, making this methodology very useful for the rapid synthesis of analogues.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Merck Frosst Center for Therapeutic Research, and the University of Toronto. We thank Solvias AG for the supply of rhodium catalyst and chiral ligands as well as initial support of this study. C.L. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship. M.K.B. thanks the German Academic Exchange Service (DAAD) for a postdoctoral fellowship. We cordially thank Dr. Jacki A. Kitching and Dr. Marion Davoust for helpful discussions.

Supporting Information Available. Full characterization details including ^1H and ^{13}C NMR, IR, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) $AlCl_3$ was used as Lewis acid.
(14) The reaction was carried out in dioxane at 80 °C for 20 h.
(15) Substrate ***syn*-48** was prepared via an oxidation−reduction sequence starting from ***anti*-48**.