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Iron-Catalyzed [3 + 2] Annulation of Aminocyclopropanes with Aldehydes: Stereoselective Synthesis of Aminotetrahydrofurans

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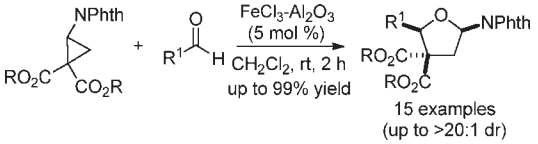
ABSTRACT



The first method for the [3 + 2] annulation of donor−acceptor aminocyclopropanes with aldehydes is reported. The reaction is catalyzed by iron trichloride on alumina in yields up to 99% and with excellent *cis* selectivities (up to >20:1) and represents a stereoselective and atom economic access to valuable 2-aminotetrahydrofurans, which constitute the core of DNA and RNA.

Donor−acceptor (D−A) cyclopropanes represent versatile three-carbon zwitterionic synthons[1] and are widely used to assemble carbocycles and heterocycles by means of [3 + *n*] annulation reactions.[2] Among them, the [3 + 2] reaction with olefins,[3] carbonyls,[4] and imines[5] represents a valuable tool for the convergent synthesis of cyclopentanes, tetrahydrofurans,[6] and pyrrolidines, respectively.

The annulation of D−A cyclopropanes with carbonyl compounds in particular has been hampered for a long time by modest diastereoselectivity and the need for stoichiometric amounts of a strong Lewis acid (i.e., TiX_4, SnX_4).[7] In the past decade, this transformation has been the focus of a renewed research effort. In particular, Johnson et al. developed catalytic methods for the highly stereoselective synthesis of tetrahydrofurans (THFs) using Lewis acids (i.e., $Sn(OTf)_2$, $Hf(OTf)_4$) under mild conditions.[8]

In the [3 + 2] annulation with aldehydes and ketones, D−A cyclopropanes bearing oxygen donor group(s) were

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(6) For a review on the synthesis of tetrahydrofurans, see: Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.

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most frequently exploited,[4b−g,8e] but the use of aryl,[4a,8a,c] alkenyl,[8b,d] alkyl,[4a,8d] and silylmethyl[2c] donors has also been documented. To the best of our knowledge, this transformation has never been reported using D−A cyclopropanes substituted with a nitrogen-containing donor group instead.[9] In fact, aminocyclopropanes are generally underrepresented in annulation and cyclization reactions,[10] despite the abundance of synthetic methods for their preparation.[11]

The development of [3 + 2] annulations of aminocyclopropanes with aldehydes would constitute important progress in the field, as this reaction allows the one-pot, atom-economic assembly of 2-aminotetrahydrofurans, a common motif in "evolutionarily selected" molecules such as nucleosides, as well as in synthetic drugs such as AZT (**1**)[12] (Figure 1).

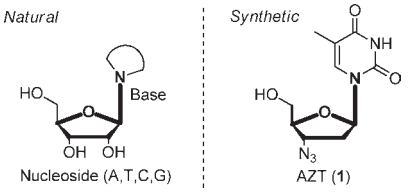


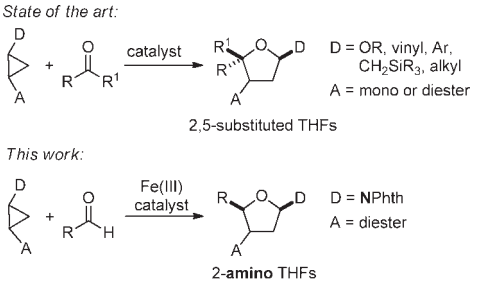
Figure 1. Bioactive natural and synthetic compounds containing an aminotetrahydrofuran core.

It is well-known that nucleosides and their mimetics[13] are widespread as therapeutic agents for the treatment of cancer, infections, and viral diseases. Therefore the 2-aminotetrahydrofuran core may be rightly considered as a privileged scaffold for drug discovery.

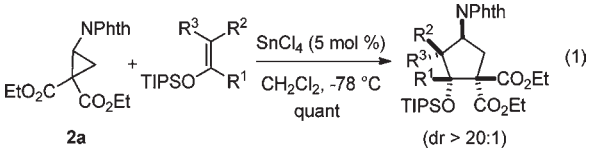
Herein, we describe the first catalytic method for the [3 + 2] annulation of donor−acceptor aminocyclopropanes with aldehydes affording 2-aminotetrahydrofurans with excellent diastereoselectivity (Scheme 1).

Our group has been interested in the use of D−A cyclopropanes (D = NPg or aryl, Pg = protecting group) as precursors of reactive intermediates in cyclization reactions onto electron-rich olefins or heterocycles.[14] In particular, we made use of aminocyclopropanes as acyl iminium precursors in the synthesis of natural alkaloids.[14b]

Scheme 1. [3 + 2] Annulation of D−A Aminocyclopropanes with Aldehydes



In 2011, we decided to investigate the use of more convergent annulation reactions of aminocyclopropanes for the efficient synthesis of carbo- and heterocycles. As a result of these efforts, we reported the first catalytic, enantiospecific [3 + 2] annulation between silyl enol ethers and D−A aminocyclopropane **2a** to give cyclopentylamines (eq 1).[15]



(1)

The fine-tuning of the D−A substituents on **2a** was required to reach an optimal compromise between stability and reactivity. We found that the combination of phthalimide as a weak donor group and a *gem*-diester as an acceptor to be ideal. As an extension to our work, we wondered if phthaloyl aminocyclopropane **2a** could be exploited in the [3 + 2] reaction with other partners, such as carbonyls.

We decided to examine first the reaction of **2a** with benzaldehyde (**3a**). In contrast to the results obtained with enol ethers, the use of tin tetrachloride (eq 1) was not ideal, since a low yield was observed at rt, while irreproducible results were obtained at −78 °C (Table 1, entries 1−2). We consequently decided to screen a more extended selection of Lewis acids. Pleasingly, all Lewis acids tested, except $Yb(OTf)_3$ (entry 3, Table 1), were competent catalysts for

(7) Only two catalytic methods were reported before 2005: References 4f−4g.

(8) Enantiospecific annulation: (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (b) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. DyKAT: (c) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. With quaternary stereocenters: (d) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996. Recently, an example of intramolecular annulation was also reported by Wang and co-workers: (e) Xing, S.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2011**10.1002/anie.201106368.

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(10) Intermolecular: (a) Wimalasena, K.; Wickman, H. B.; Mahindaratne, M. P. D. *Eur. J. Org. Chem.* **2001**, *2001*, 3811. (b) Tanguy, C.; Bertus, P.; Szymoniak, J.; Larionov, O. V.; de Meijere, A. *Synlett* **2006**, *2006*, 2339. Intramolecular: (c) Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322. (d) Larquetoux, L.; Ouhamou, N.; Chiaroni, A.; Six, Y. *Eur. J. Org. Chem.* **2005**, *2005*, 4654. (e) Mangelinckx, S.; De Kimpe, N. *Synlett* **2006**, *2006*, 0369. Applications in total synthesis: (f) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (g) De Simone, F.; Waser, J. *Synlett* **2011**, *2011*, 589.

(11) Recent examples: (a) Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 1987. (b) Song, Z. L.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C. H.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069. (c) Valenta, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 14179 and references therein.

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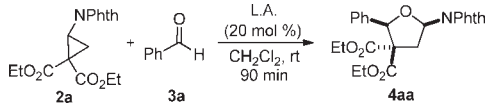
(13) Herdewijn, P. *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*; Wiley-VCH: Weinheim, 2008.

(14) (a) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023. (b) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767.

(15) De Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. Aminocyclopropane **2a** can be synthesized in multigram scale *via* rhodium-catalysed cyclopropanation of commercially available vinylphthalimide with diethyl diazomalonate.

the activation of **2a**, affording 2-aminotetrahydrofuran **4aa** in excellent diastereoselectivity in favor of the *cis* isomer (entries 4−11). Employing $In(OTf)_3$, a trace of the *trans* isomer could be identified in the crude ^1H NMR spectrum (dr = 19:1, entry 4); otherwise only the 2,5-*cis*-tetrahydrofuran[16] was detected. Cyclopropane **2a** was completely consumed after 90 min in all cases, except for $Cu(OTf)_2$ (entry 5).

Table 1. Screening of Lewis Acids[a]



entry	Lewis acid	yield (%)[b]	dr (*cis*:*trans*)[c]
1	$SnCl_4$	46	>20:1
2[d]	$SnCl_4$	70-100	>20:1
3	$Yb(OTf)_3$	n.r.	-
4	$In(OTf)_3$	72	19:1
5[e]	$Cu(OTf)_2$	50	>20:1
6	$InCl_3$	74	>20:1
7	AuCl	91	>20:1
8	$Sn(OTf)_2$	82	>20:1
9	$Hf(OTf)_4$	100	>20:1
10	$Sc(OTf)_3$	100	>20:1
11	$FeCl_3$-Al_2O_3	100	>20:1

[a] Reaction conditions: 1.0 equiv of **2a**, 1.5 equiv of **3a**, 20 mol % of Lewis acid, 0.1 M in dichloromethane. [b] Yield was determined via ^1H NMR spectroscopy using hexamethyldisiloxane as internal standard. [c] Determined by ^1H NMR spectroscopy on the crude raction mixture. [d] Performed at −78 °C. [e] Only 50% conversion of **2a** was observed.

The effect of the counteranion was studied in the case of indium salts, and it proved negligible (triflate vs chloride, entry 4 vs 6). When the formation of 5-membered ring **4aa** was not quantitative (entries 1−2, 4−8), the crude ^1H NMR spectrum showed the presence of a byproduct, most likely derived from decomposition of the Lewis acid activated **2a**. The cleanest reactions were observed with $Hf(OTf)_4$, $Sc(OTf)_3$, and $FeCl_3-Al_2O_3$ (entries 9−11).[17] We selected the latter as a catalyst to continue our studies due to its low cost and toxicity.[18] Although the efficiency of Fe catalysts in promoting cycloaddition and ring expansion is well established,[19] this represents the first example of an Fe-catalyzed [3 + 2] annulation of D−A cyclopropanes.

(16) 2,5-Relative stereochemistry was assigned on the basis of X-ray diffraction analysis performed on compound **4ab** and extended to the other compounds of the series on the basis of the regularity in their NMR spectra (see Figure 3 and Supporting Information for details).

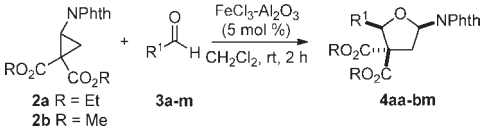
(17) Iron trichloride gave comparable results, but the alumina-supported reagent was preferred because it is easier to handle and known to be a scavenger of adventitious traces of water and acid. For examples on the use of $FeCl_3-Al_2O_3$, see: (a) Tietze, L. F.; Beifuss, U. *Synthesis* **1988**, *5*, 359. (b) Tietze, L. F.; Beifuss, U.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed.* **1988**, *27*, 703.

(18) In the past decade, a revival of iron catalysis in organic synthesis was observed, due to the abundance and versatility of this environmentally benign metal. See for example: *Iron Catalysis Fundamentals and Applications*; Plietker, B., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin Heidelberg, 2011; Vol. 33.

(19) (a) Hilt, G.; Janikowski, J. *Iron Catalysis in Organic Chemistry: Reactions and Applications*; Wiley-VCH: Weinheim, 2008; Chapter 9. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev* **2004**, *104*, 6217.

Next, the scope of the reaction with **2a** and **2b** was explored, using 5 mol % of iron(III) chloride on alumina and 1.5 equiv of aldehydes **3a**−**m** at rt (Table 2).

Table 2. Scope of Aldehydes **3a**−**m** in the [3 + 2] Annulation with Aminocyclopropanes **2a**−**b**[a]



entry	R	R'	yield (%)	dr[b,c] (*dr*)[d]
1(**4aa**)	Et	Ph (**3a**)	94	>20:1
2(**4ba**)	Me	Ph (**3a**)	95	>20:1
3(**4ab**)	Et	4-$MeOC_6H_4$ (**3b**)	97	6:1
4(**4bc**)	Me	2-$MeOC_6H_4$ (**3c**)	83	5:1
5(**4bd**)	Me	2-thienyl (**3d**)	84	5:1
6(**4ab**)[e]	Et	4-$MeOC_6H_4$ (**3b**)	98	9:1(*>20:1*)
7(**4bc**)[e]	Me	2-$MeOC_6H_4$ (**3c**)	92	17:1 (*>20:1*)
8(**4bd**)[e]	Me	2-thienyl (**3d**)	89	>20:1
9(**4be**)	Me	4-ClC_6H_4 (**3e**)	91	>20:1
10(**4bf**)	Me	4-$NO_2C_6H_4$ (**3f**)	71	>20:1
11(**4bg**)	Me	(*E*)-CH=CHPh (**3g**)	94	2.5:1
12(**4bg**)[e]	Me	(*E*)-CH=CHPh (**3g**)	95	10:1(*>20:1*)
13(**4ah**)	Et	(*E*)-$CH=CHC_3H_7$ (**3h**)	99	10:1(*>20:1*)
14(**4bh**)	Me	(*E*)-$CH=CHC_3H_7$ (**3h**)	95	7:1(*>20:1*)
15(**4ai**)	Et	*n*-Pr (**3i**)	94	9:1(*>20:1*)
16(**4bj**)	Me	CH_2CH_2Ph (**3j**)	89	>20:1
17(**4ak**)	Et	*i*-Pr (**3k**)	99	7:1
18(**4al**)	Et	Cyclohexyl (**3l**)	90	7:1
19(**4bm**)	Me	*t*-Bu (**3m**)	92	9:1(*>20:1*)

[a] Standard reaction conditions: 0.2 mmol of **2a**−**b**, 1.5 equiv of **3a**−**m**, 5 mol % of $FeCl_3-Al_2O_3$, 0.1 M in dichloromethane. [b] Expressed as *cis*/*trans*. [c] Determined by ^1H NMR spectroscopy on the crude raction mixture. [d] Obtained after one single recrystallization (see Supporting Informations). [e] Reaction run at −10 °C.

In general, excellent yields were obtained in a short reaction time (2 h),[20] while employing aldehydes with diverse steric and electronic properties. No difference in reactivity/selectivity was observed between the ethyl diester **2a** and the methyl diester **2b** in the reaction with benzaldehyde (**3a**) (entry 1 vs 2). The electron-rich *para*- and *ortho*- anisaldehydes (**3b**−**c**) and thiophene-2-carboxaldehyde (**3d**) displayed modest stereoselectivities at rt(up to 6:1 *cis*/*trans*; entries 3−5); nevertheless increased dr's were obtained at a lower temperature (up to >20:1 *cis*/*trans*, entries 6−8). Interestingly, no detrimental effect on yield and stereoselectivity of an *ortho vs para* substituent was observed with anisaldehyde **3c** vs **3b** (entries 6−7). In all cases, the two isomers could not be separated by flash chromatography. However, the pure *cis* isomer could be obtained by means of a single recrystallization, except for products **4ak** and **4al**. The X-ray diffraction analysis performed on aminotetrahydrofuran **4ab** allowed the unambiguous attribution of the 2,5-*cis* relative stereochemistry (Figure 2).

(20) 2 h was the chosen standard time for full conversion. When completion was reached in a shorter time, the prolonged stirring with the catalyst at rt caused no erosion in yield or dr.

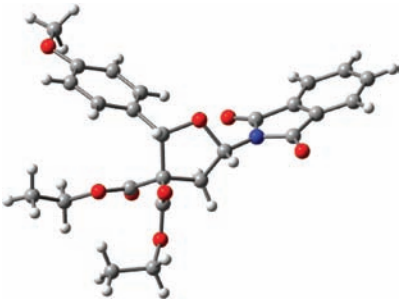
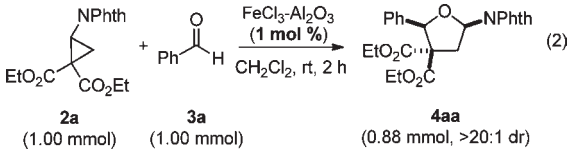


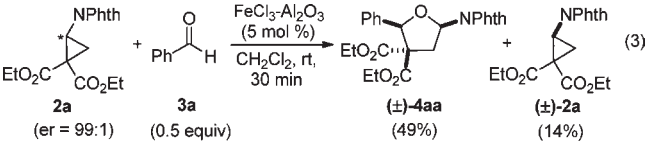
Figure 2. X-ray structure of aminotetrahydrofuran **4ab**.

The annulation reaction was not limited to aromatic aldehydes, and a good yield was also obtained in the case of cinnamyl aldehyde (**4bg**), albeit with a low diastereoselectivity (entry 11). Once again, the *cis*-selectivity could be increased by lowering the temperature to −10 °C (entry 12). The reaction was also successful for unsaturated aldehyde **3h**, with both **2a** and **2b** (entries 13 and 14). Aliphatic aldehydes are generally challenging substrates for Lewis acid catalyzed reactions, as they are prone to undergo aldol side reactions. Gratifyingly, this was not an issue under our mild reaction conditions, and aliphatic aldehydes with linear (entries 15−16) or branched (entries 17−19) substituents afforded the corresponding aminotetrahydrofurans in outstanding yields (89−99%) and good diastereoselectivities (up to > 20:1 *cis*/*trans*).

As further evidence of the efficiency of our methodology, the reaction of **2a** with an equimolar amount of benzaldehyde (**3a**) in the presence of a 1 mol % loading of Fe catalyst afforded compound **4aa** in 88% yield and excellent dr on a 1 mmol scale (eq 2).



To gain more knowledge on the mechanism of our [3 + 2] annulation, enantioenriched **2a** (er = 99:1)[21] was reacted with **3a** under the standard reaction conditions (eq 3). We had found in our previous work that the reaction of enantiopure aminocyclopropane **2a** with silyl enol ethers was enantiospecific with all the olefins tested,[15] indicating most probably the formation of a tight, configurationally stable ion pair between the cyclopropane and the tin catalyst. In contrast, the iron-catalyzed annulation of **2a** with benzaldehyde (**3a**) at rt resulted in a complete loss of the stereochemical information, as tetrahydrofuran **4aa** was isolated in a racemic form.[8b,22] This evidence suggests that, upon Lewis acid activation, the aminocyclopropane undergoes fast racemization *via* an open, zwitterionic species. While the result hampers the synthesis of enantioenriched amino THFs, it is a potential starting point for the development of a dynamic kinetic asymmetric transformation (DyKAT).[8c,23]



In summary, we have developed the first iron(III) catalyzed [3 + 2] annulation of aminocyclopropanes with aldehydes, affording aminotetrahydrofurans in excellent yields (71−99%) and diasteroselectivities (up to > 20:1 dr). This protocol represents an atom-economic, stereoselective route to unprecedented structures that share an aminotetrahydrofuran motif of utmost value, due to its presence in DNA and RNA. The exploration of the synthetic potential of the aminotetrahydrofurans,[24] the development of an asymmetric version of the reaction, and its extension to ketones are currently under investigation in our laboratories.

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Supporting Information Available. Experimental details, characterization data, and X-rays diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Obtained by preparative HPLC separation on chiral stationary phase (see Supporting Information for details).

(22) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597.

(23) (a) Pellissier, H. *Chirality from dynamic kinetic resolution*; RSC Publishing: Cambridge, 2011. (b) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060.

(24) The ring opening of phthalimide with amines was accomplished, but cleavage of the second C−N bond could not yet be achieved due to the instability of the resulting free aminotetrahydrofuran. As alternative strategies, the use of modified aminocyclopropanes or the substitution of the phthalimide with nucleophiles will be investigated in the future for the synthesis of nucleoside analogues.