Piperidines from acid-catalysed cyclisations: Pitfalls, solutions and a new ring contraction to pyrrolidines

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abstract

The success of acid-catalysed cyclisations of alka-4-enylamine derivatives to piperidines depends very much on the nature of the amine protecting group: while carbamates and related amides can usually be readily and cleanly transformed, the corresponding sulfonamides react further by ring contraction leading to pyrrolidines, especially when such substrates are sterically crowded.

Although arguably counter-intuitive, it has been found possible to realise good to excellent yields of pyrrolidines by acid-catalysed cyclisations of unsaturated amine derivatives,[1] in our case in reac-tions initially directed towards the elaboration of the highly substi-tuted proline analogues 2 from the amino-ester derivatives 1 (Scheme 1), along with tetrahydroisoquinolines.[2] Overall, such transformations can be viewed as intramolecular hydroamina-tions[3] and so, not surprisingly, a number of examples of related intermolecular hydroaminations, induced under such acidic condi-tions, have also been reported.[4]

In most examples, be these inter- or intra-molecular, additions of carbamates or sulfonamides to unactivated alkenes require exposure of the precursor(s) to strongly acidic conditions, typically obtained using 0.1–0.5 equivalents of concentrated sulfuric acid or the super acid trifluoromethanesulfonic (triflic) acid, usually in either a chloroalkane or toluene. Current views on the mechanism of such hydroaminations form a consensus that the best descriptor consists of additions of a proton and the nitrogen atom to the alkene in a concerted if asynchronous fashion. Alternative stepwise processes seem much less likely.[5] In our work, the asynchronous nature of the cyclisations was consistent with an observed direct relationship between the ease of reaction and carbenium ion sta-bility: thus, the prenyl derivative 1a underwent cyclisation in a few minutes at ice bath temperatures whereas the cinnamyl derivative 1b required a few hours at ambient temperature and the crotyl analogue 1c only reacted when heated to 60 LC.[2]

An extension to this methodology to the elaboration of piperidi-nes 4 (Scheme 2) seemed viable, especially as the necessary pre-cursors 3 were readily available using a variety of flexible approaches; some evidence that this could indeed be the case had already been provided by Hartwig and Schlummer[1] (see later).

Our initial studies focussed on the cyclisation behaviour of pre-cursors 5 and 6, obtained by alkylation of the carbanion 7[6] using the corresponding homoallylic halides followed by protecting group exchange (Scheme 3). The logic behind our choice was that, whatever the mechanistic subtleties, the intermediacy of even a partly formed, tertiary carbenium ion should be favoured in such substrates.

However, molecular life is often not so simple: upon exposure to triflic acid (0.6 equiv.) in dichloromethane at ambient tempera-ture, both precursors 5 and 6 were unexpectedly converted into the corresponding pyrrolidines 8 and 9 (Scheme 4).

To make certain of our structural assignments, an authentic sample of pyrrolidine 8 was synthesised from the known precursor 10 by sequential iodocyclisation[7] to give the iodo-pyrrolidine 11 and hydrogenolytic removal of the iodine atom, which provided pyrrolidine 8, albeit in a different ratio of isomers to that obtained from the acid-catalysed cyclisation (Scheme 5). Despite this, the forgoing structural assignments 8 and 9 were clearly correct based on comparative ^{1}H and ^{13}C NMR data.

Wondering if the ester group was playing some unanticipated role, we examined similar acid-catalysed cyclisations of the less

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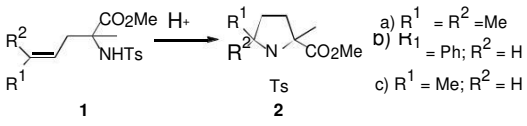
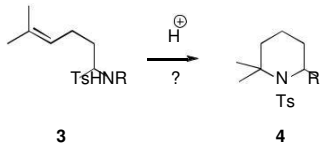
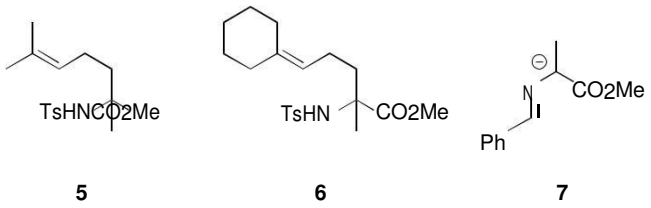


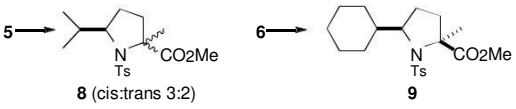
Scheme 1. An acid-catalysed approach to highly substituted prolines.



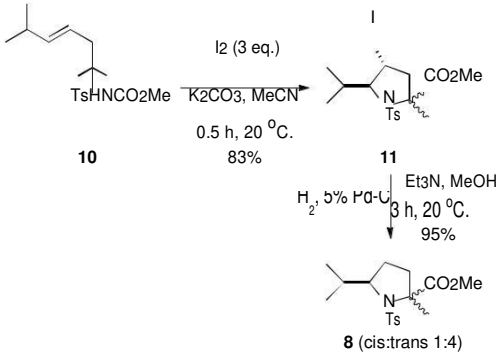
Scheme 2. An extension to piperidine synthesis?



Scheme 3. Model precursors 5 and 6 prepared using carbanion 7.



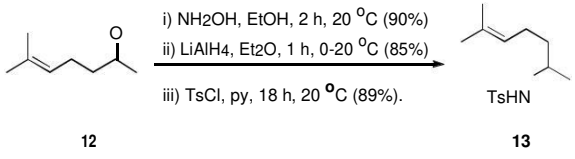
Scheme 4. Unexpected formation of pyrrolidines 8 and 9 from precursors 5 and 6. Reagents and conditions: triflic acid (0.6 eq.), CH_2Cl_2, 20 LC, 1 h; yields > 90%.



Scheme 5. Structural proof using a known iodocyclisation.[7]

functionalised sulfonamide 13, which was readily and efficiently synthesised from the commercial ketone 12 by sequential oxima-tion, reduction and tosylation reactions (Scheme 6).

All attempts at cyclisation of the precursor 13 resulted in the formation of mixtures of the desired piperidine 14 together with



Scheme 6. Synthesis of a simpler piperidine precursor 13.

the starting amino-alkene and/or the pyrrolidine 15 (Table 1). The results shown are a representative summation of many exper-iments in which variations to the acid (c. H_2SO_4 or TfOH), its quan-tity, and to the reaction temperature and time all resulted in the formation of mixtures. The products, 14 and 15, could be separated by column chromatography and were fully characterized.[8,9]

There was clearly only a very narrow window of opportunity available for the formation of piperidine 14 and then only as a major product. Significantly, when a separated sample of the latter was re-exposed to the acidic conditions, it was rapidly converted into the pyrrolidine 15, indicating that it was a genuine intermedi-ate between the precursor 13 and pyrrolidine 15. This led us to propose the mechanism shown in Scheme 7 as an explanation for the results given in Table 1. An initial cyclisation of the precur-sor 13 does indeed lead to the piperidine 14, by formation of an electron-deficient species, here represented by the carbenium form 16, but that this is an equilibration, brought about by N-protona-tion. An alternative, less favoured pathway leads, by way of the secondary carbenium ion 17, to the pyrrolidine 15 which, crucially, is not in equilibrium with its precursor carbenium ion, and hence is the thermodynamically favoured product.

This led us to wonder if this chemistry could constitute a new type of ring contraction for the conversion of piperidines into pyrrolidines; the results thus far obtained are presented in Table 2. As shown above (Table 1), the essentially quantitative yield of pyrrolidine 15 suggested that the 2,2-dimethyl analogue (Entry
1) should also undergo such a contraction. It did, but more slowly and less efficiently. That the considerable steric crowding present in piperidine 14 is a key factor was exemplified by the very slow conversions of the 2-substituted piperidines into the correspond-ing pyrrolidines (Entries 2, and 3). A 2,6-disubstituted piperidine (Entry 4) underwent more rapid contraction, leading to a useful synthetic yield of the corresponding pyrrolidine, while piperidines unsubstituted adjacent to nitrogen were essentially inert (Entries 5, and 6). Finally, the bulkier 2-cyclohexylpiperidine (Entry 7) reacted slowly but cleanly while the 2-phenyl derivative (Entry

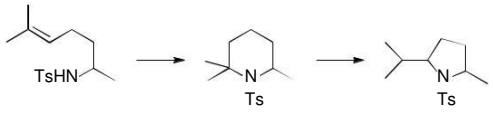
8) underwent slow decomposition, possibly involving transfer of
the sulfonyl group to the phenyl ring, a tentative conclusion based only on ^1H NMR data obtained for crude samples.[10]

The stability of sulfonamide groups and of piperidines in gen-eral combine to suggest that N-tosylpiperidines are similarly stable
– these results clearly show that they are not, at least under these quite extreme acidic conditions. We do not claim that this is a syn-thetically useful ring contraction, except in examples of piperidines which are highly substituted in the 2- and 6-positions, but we do highlight it as a potential source of material loss in synthetic steps
involving heating such piperidines under acidic conditions. Results reported by Hartwig and Schlummer[1] confirm that the use of a sul-fonamide protecting group was not optimal and is consistent with our observations shown in Table 2, although the stability of 2-phe-nyl-1-tosylpiperidine is at variance (Scheme 8).

A number of methods for achieving ring contractions of piperidines have been reported over the years. Most commonly,
these rely on the formation of an intermediate aziridinium ion and attack of a nucleophile.[11] Such reactions closely resemble a Favorskii rearrangement[12] and can also be carried out photochem-ically[13] and enzymatically.[14] The present method, while limited, appears to be novel.

In a bid to alter the electronics of the sulfonyl group, we tested the 4-nosyl (4-nitrophenylsulfonyl, 4-Ns) group highlighted by
Fukuyama and co-workers, which has the useful property of being removed by exposure to thiolate ions.[15] In the event, the change had little effect: a selection of results is presented in Table 3. There were few differences to those obtained from the N-tosyl deriva-tives (Table 1), despite the electronic differences of Ts and Ns groups; the combined chemical yields were again very high. In

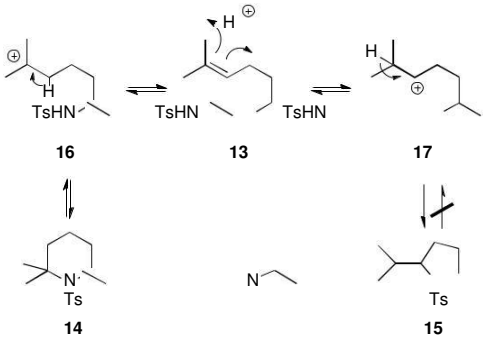
Table 1
Acid catalysed cyclisation and contraction of precursor 13.



13 14 15

Precursor	Time min.	Temp LC	Acid (equiv.)	Ratio of 13:14:15
13	6	20	TfOH (0.3)	48:7:45
13	60	20	TfOH (0.3)	0:0:100
13	15	0	c.H_2SO_4 (0.4)	5:85:10
13	60	0	c.H_2SO_4 (0.4)	25:73:2
13	90	10	TfOH (0.4)	53:35:12
13	120	30	TfOH (0.4)	75:18:7
13	180	60	TfOH (0.4)	100:0:0
14	5	20	c.H_2SO_4 (0.4)	10:85:5
14	15	20	c.H_2SO_4 (0.4)	0:25:75
14	45	20	c.H_2SO_4 (0.5)	0:7:93
14	75	20	c.H_2SO_4 (0.5)	0:0:100

All reactions were carried out in dry dichloromethane and worked up by adding a slight excess of aq. 3 M K_2CO_3, separation and evaporation.
All product mixtures were isolated in 95% yields, according to weight and NMR data.



Scheme 7. An explanation for the results shown in Table 1.

contrast, methanesulfonyl (Ms) derivatives were unstable to the acidic conditions.

We therefore turned to using carbonyl-based N-protecting groups.[16] Initial attempts using trifluoroacetyl derivatives also failed due to their instability to the acidic conditions. Similarly, while both N-acetyl[1] and N-phenacyl derivatives underwent some decomposition, we were pleased to note that cyclisations of such derivatives led only to piperidines uncontaminated by pyrro-lidines. We were delighted to then discover that the methyl carbamate 21 underwent rapid cyclisation at 0 LC upon exposure to 0.4 equivalents of either sulfuric or triflic acid in dichloromethane to provide excellent yields of the piperidine 22 (Scheme 9). Nota-bly, if the isolated piperidine 28 was returned to the acidic condi-tions for a prolonged period (24 h) at ambient temperature, there

Table 2
Acid catalysed ring contraction of N tosylpiperidines.

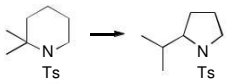
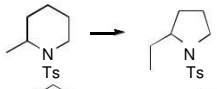
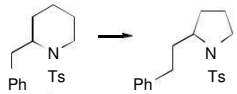
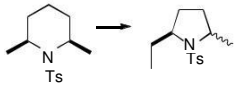
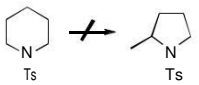
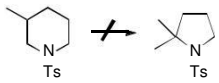
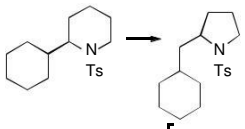
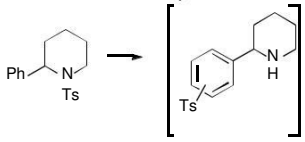
Entry	Piperidine	Pyrrolidine	Conditions[a]	Yield of Pyrrolidine[b]
1			0.5 eq. TfOH, 25 h	80%
2			0.2 eq. c.H_2SO_4, 72 h 0.6 eq. c.H_2SO_4, 24 h 0.5 eq. TfOH, 72 h	9% 21% 5%
3			0.5 eq. TfOH, 24 h 2.0 eq. TfOH, 24 h 0.5 eq. TfOH, 72 h 0.4 eq. c.H_2SO_4, 24 h	30% 57% 44% 27%
4			0.4 eq. c.H_2SO_4, 3 h 0.4 eq. c.H_2SO_4, 24 h 0.3 eq. c.H_2SO_4, 72 h 0.5 eq. TfOH, 72 h	54% (28:26)[c] 72% (50:22) 57% (43:14) 38% (15:23)
5			0.5 eq. TfOH, 72 h	0%

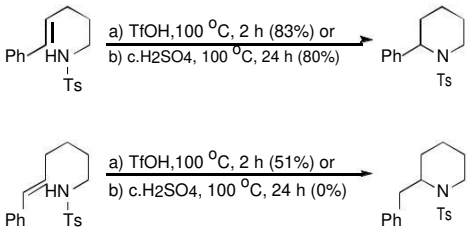
Table 2 (continued)

Entry	Piperidine	Pyrrolidine	Conditions[a]	Yield of Pyrrolidine[b]
6			0.5 eq. TfOH, 72 h	0%
7			0.4 eq. TfOH, 24 h 0.4 eq. TfOH, 48 h 0.4 eq. c.H_2SO_4, 23 h	32% 48% 23%
8			0.5 eq. TfOH, 72 h [slow decom[n]]	

[a] All reactions were carried out in toluene heated at reflux.

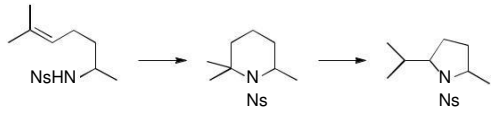
[b] Remainder unreacted piperidine; total yield > 95%.

[c] cis/trans ratios.



Scheme 8. Hartwig and Schlummer's results, using 20 mol% of each acid in toluene (Ref. 1).

Table 3
Using 4 nosyl in place of tosyl.



18 **19** **20**

Time min.	Temp. LC	Ratio of 18:19:20
60	0	48:46:6
180	0	15:66:19
20	20	13:9:78
60	20	0:0:100

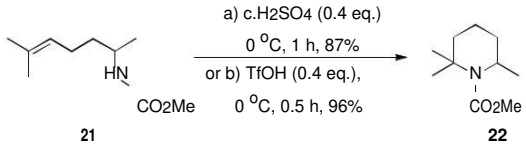
Reagents and conditions: c.H_2SO_4 (0.5 eq.), CH_2Cl_2.
All overall yields were >95%.

was no sign of either decomposition or contraction to the corre-sponding pyrrolidine.

Remarkably, given its sensitivity to acidic conditions, a Z-carba-mate group also survived the acidic conditions required for cyclisa-tion: the benzyl derivative **23** was converted into piperidine **24** following very brief exposure to sulfuric acid (0.4 equiv.) in excel-lent yield (Scheme 10).

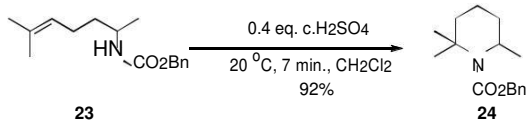
In contrast, the cinnamyl derivative **25** required prolonged exposure to acid at ambient temperature to provide an excellent yield of the piperidine **26**, again unaccompanied by any pyrrolidi-nes (Scheme 11).

The cis-diastereoisomer **26** was formed exclusively; both sub-stituents occupied axial positions, according to ^{1}H NMR data,
which indicated that neither proton adjacent to nitrogen could be in an axial position.[17,18] However, if there was competition
between the products, as usual, the overall 5-exo pathway was



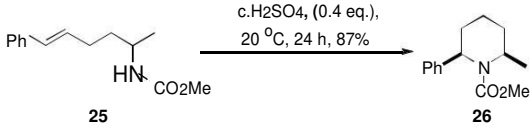
21 **22**

Scheme 9. Optimized cyclisations of methyl carbamate **21**.



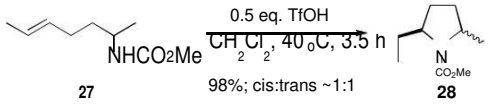
23 **24**

Scheme 10. With care, even a 'Z' carbamate survives.



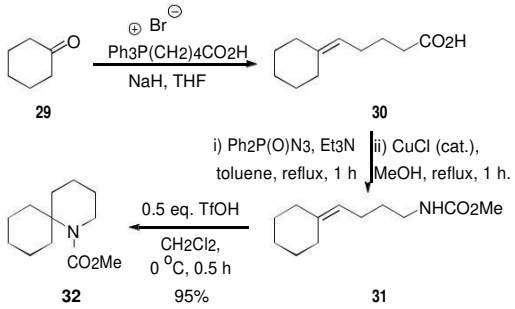
25 **26**

Scheme 11. Optimized conditions for cyclisation of the cinnamyl derivative **25** to give the cis-piperidine **26**.



27 **28**

Scheme 12. Overall 5-exo cyclisation is favoured over 6-endo.



29 **30** **31** **32**

Scheme 13. An application to spiro-piperidine synthesis.

favoured: thus, the unsaturated carbamate 33 was converted exclusively into pyrrolidine 34 (Scheme 12).

In a final illustration, we have shown that spiro-piperidines can also be made in this way. Wittig homologation of cyclohexanone 29 gave the cyclohexylidenecarboxylic acid 30,[19] Curtius rear-rangement of which[20] then led to the required cyclisation precur-sor 31. Brief exposure to triflic acid (0.5 equiv.) at 0 LC led to a 95% yield of the spiro-piperidine 32 (Scheme 13).

Despite the strongly acidic conditions required, both for the ring contractions and the piperidine syntheses, these examples show that this simple methodology can be highly effective for the elab-oration of many types of pyrrolidine and piperidine derivatives, especially sterically crowded examples. Further work is in progress to expand the utility of this methodology, especially with a view to allowing the incorporation of more functional groups.[21]

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References

1. Schlummer B, Hartwig JF. Org Lett. 2002;4:1471–1473.
2. Haskins CM, Knight DW. Chem Commun. 2002;2724–2725; Griffiths-Jones CM, Knight DW. Tetrahedron. 2010;66:4150–4166; Griffiths-Jones CM, Knight DW. Tetrahedron. 2011;67:8515–8528; Henderson L, Knight DW, Williams AC. Tetrahedron Lett. 2012;53:4657–4660; Henderson L, Knight DW, Williams AC. Synlett. 2012;1667–1669;
Ghanim AM, Knight DW, Rutkowski PM, Osman NA, Abdel-Fattah HA, Kadry AM. Tetrahedron Lett. 2017;58:294–297.
3. Mueller TE, Hultzsch KC, Yus M, Foubelo F, Tada M. Chem Rev. 2008;108:3795–3892.
4. For intermolecular examples, see Zhang J, Yang C, He C. J Am Chem Soc. 2006;128:1798–1799;
Marcsekova K, Doye S. Synthesis. 2007;145–154;
Rosenfeld DC, Shekhar S, Takemiya A, Utsunomiya M, Hartwig JF. Org Lett. 2006;8:4179–4182;
. These additions are related to the older Ritter reaction:Ritter JJ, Minieri PP. J Am Chem Soc. 1948;70:4045–4048;
Moran J, Cebrowski PH, Beauchemin AM. J Org Chem. 2008;73:1004–1007;
Van Emelen K, De Wit T, Hoonaert GJ, Compernolle F. Tetrahedron. 2002;58:4225–4236;
. For a review, seeKrimen LI, Cota DJ. Org React. 1969;17:213–325.
5. Li X, Ye S, He C, Yu ZX. Eur J Org Chem. 2008;4296–4303;
Kovacs G, Lledos A, Ujaque G. Organometallics. 2010;29:5919–5926;
Brooner REM, Widenhoefer RA. Chem Eur J. 2011;17:6170–6178;
Li HX, Wen MW, Lu G, Wang Z-X. Dalton Trans. 2012;41:9091–9100.
6. Stork G, Leong AY, Touzin AM. J Org Chem. 1976;41:3491–3493.
7. Jones AD, Knight DW, Hibbs DE. J Chem Soc, Perkin Trans 1. 2001;1182–1203.
8. The structure of pyrrolidine 15 was secured by comparative data (Refs. 7,9). The piperidine structure 14 was verified by analysis of its spectroscopic data and comparisons with later compounds.
9. Jones AD, Knight DW, Redfern AL, Morgan IR, Williams AC. Tetrahedron. 2006;62:9247–9257.
10. For a recent example, see Han R, He L, Liu L, Xie X, She X. Chem Asian J. 2016;11:193–197.
11. For reviews, see Gomez Pardo D, Cossy J. Chemtracts. 2002;15:579–605; Lu P. Tetrahedron. 2010;66:2549–2560;
Metro T-X, Duthion B, Gomez Pardo D, Cossy J. Chem Soc Rev. 2010;39:89–102;
Stankovic S, D'Hooghe M, Catak S, et al. Chem Soc Rev. 2012;41:643–665; Gomez Pardo D, Cossy J. Chem Eur J. 2014;20:4516–4525;
. For recent contributions, seeBandarage UK, Davies RJ. Tetrahedron Lett. 2010;51:6415–6417;
Dolfen J, Kenis S, Van Hecke K, DeKimpe N, D'Hooghe M. Chem Eur J. 2014;20:10650–10653;
Feraldi-Xypolia A, Gomez Pardo D, Cossy J. Chem Eur J. 2015;21:12876–12880. and references therein.
12. See, for example, Sosnovsky G, Cai ZW. J Org Chem. 1995;60:3414–3418; Babic A, Pecar S. Synlett. 2008;1155–1158;
Wu H, Coble V, Vasalatiy O, Swenson RE, Krishna MC, Mitchell JB. Tetrahedron Lett. 2014;55:5570–5571. and references therein.
13. Drouin A, Winter DK, Pichette S, Aubert-Nicol S, Lessard J, Spino C. J Org Chem. 2011;76:164–169.
14. Yin W, Doss GA, Stearns RA, et al. Drug Metab Dispos. 2003;31:215–223;
Yin W, Mitra K, Stearns RA, Baille TA, Kumar S. Biochemistry. 2004;43:5455–5466.
15. Kan T, Fukuyama T. Chem Commun. 2004;353–359. and references therein.
16. For an indication that this could be successful, see van Lierop BJ, Jackson WR, Robinson AJ. Tetrahedron. 2010;66:5357–5366.
17. Examples of this phenomenon was reported some time ago: Chow YL, Colón CJ, Tam JNS. Can J Chem. 1968;46:2821–2825.
18. This has been confirmed by both NMR and X-ray analysis, details of which will be reported later: Aldmairi AH, Kariuki B, Knight DW. Unpublished Results.
19. Avlonitis N, Lekka E, Detsi A, et al. J Med Chem. 2003;46:755–767.
20. Duggan ME, Imagire JS. Synthesis. 1989;131–132.
21. For examples of similar cyclisations, induced using Lewis acids, see Komeyama T, Morimoto T, Takaki K. Angew Chem Int Ed. 2006;45:2938–2941 ($FeCl_3$); Bondalapati S, Indukuri K, Ghosh P, Saikia AK. Eur J Org Chem. 2013;952–956 (BF_3 OEt_2).