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Stereocontrolled Synthesis of Trisubstituted Cyclopropanes: Expedient, Atom-Economical, Asymmetric Syntheses of (+)-Bicifadine and DOV21947

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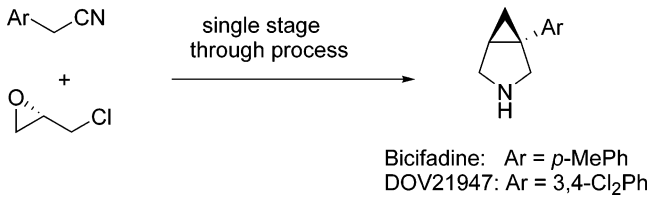
ABSTRACT



An expedient, atom-economical, asymmetric synthesis of 1-aryl-3-azabicyclo[3.1.0]hexanes, including (+)-Bicifadine and DOV21947, in a single-stage through process without isolation of any intermediates has been developed. The key of this synthesis is the in-depth mechanistic understanding of the complicated epoxy nitrile coupling at each reaction stage. Therefore, the desired trisubstituted cyclopropane can be prepared in high ee and yield by controlling the reaction pathway through manipulating the nitrile anion aggregation state.

Bicifadine (**1a**) is a potent inhibitor of both the serotonin and norepinephrine reuptake transporters and an *N*-methyl-D-aspartate (NMDA) antagonist with a nonnarcotic profile.[1] DOV21947 (**1b**) is a potent triple reuptake inhibitor, blocking the serotonin, norepinephrine, and dopamine reuptake transporters.[2] Bicifadine and DOV21947 are currently undergoing clinical evaluation[1a,2] for the treatment of pain and other diseases related to these neurotransporters, respectively.

The reported syntheses of Bicifadine and DOV21947 are racemic and inefficient.[1] Asymmetric preparation of these functionalized cyclopropanes remains a challenging topic, although several methods have been reported.[3] We envisioned that compound **1** could arise from cyclodehydration of the corresponding cyclopropylamino alcohol **2** which in turn could come from reduction of the hydroxyl nitrile **3**. This hydroxyl nitrile could potentially be derived from coupling an appropriately substituted arylacetonitrile with a chiral halohydrin (Scheme 1).

Similar transformations have been reported,[4] although the protocols are not scalable and attempts to optimize the conditions have resulted in a poor yield and/or ee.[4a] As a

(1) (a) Sorbera, L. A.; Castaner, J.; Leeson, P. A. *Drugs Future* **2005**, *30*, 7. (b) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; Hofmann, C. M.; McKenzie, T. C.; Safir, S. R.; Osterberg, A. C.; Cosulich, D. B.; Lovell, F. M. *J. Med. Chem.* **1981**, *24*, 481.

(2) Skolnick, P.; Popik, P.; Janowsk, A.; Beer, B.; Lippa, A. *Eur. J. Pharmacol.* **2003**, *461*, 99; *Life Sci.* **2003**, *73*, 3175.

(3) For a superb review, see: Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. For recent examples, see: (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (b) Zheng, J.; Liao, W.; Tang, Y.; Sun, X.; Dai, L. *J. Am. Chem. Soc.* **2005**, *127*, 12222. (c) Kim, H. Y.; Lurain, A. E.; Garcia-Garcla, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138.

(4) (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamsihita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915. (b) For a leading reference of racemic synthesis, see: Langer, P.; Freifeld, I. *Org. Lett.* **2001**, *3*, 3903 and references therein.

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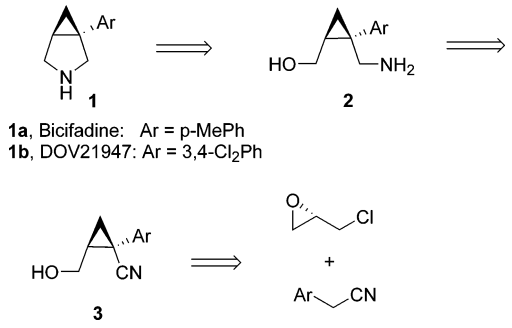
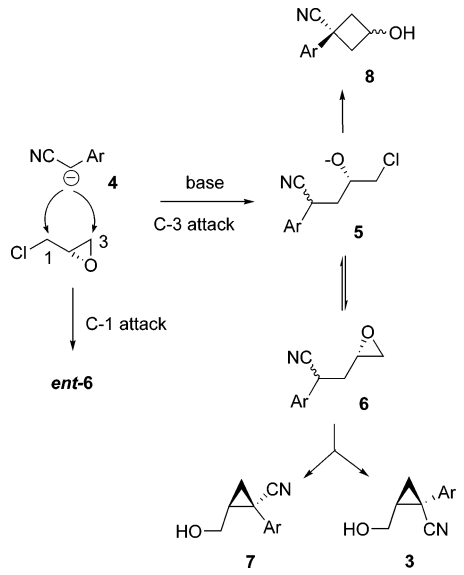
Scheme 1. Retrosynthetic Analysis



result, we decided to carry out a systematic investigation on this transformation to gain mechanistic insight and ultimately to arrive at an optimized, scaleable protocol. Scheme 2

Scheme 2. Pathways to (+)- or (−)-*cis/trans*-Cyclopropanes and (±)-Cyclobutanes



depicts the challenges for this transformation: (1) to suppress the competitive C1 attack pathway to form the enantiomer of **6** (***ent*-6**) and therefore to afford **3** in high ee; (2) to block formation of cyclobutane **8** via S_Ni ring closure of **5**; (3) to gain the cis/trans control (**3** vs **7**) of the S_Ni epoxide opening of **6**. Herein, we report our understanding of the epoxy nitrile coupling at each stage, which results in an expedient, atom-economical, asymmetric synthesis of 1-aryl-3-azabicyclo-[3.1.0]hexanes.

In an attempt to decouple these factors, the metal counterion effects were first probed utilizing substrate **4b** (Ar = 3,4-Cl_2Ph) and epichlorohydrin as summarized in Table 1. Surprisingly, the reaction pathway can be dramatically altered by the choice of counter metal ion: (1) Mg^{2+} counterions provided the achiral, *cis*/*trans*-cyclobutanes **8** presumably through the intermediacy of **5b**;[5] (2) lithium bases provided the chlorohydrin **5b** at −15 °C; however, subsequent reaction

Table 1. Counter Metal Ion Effects on Epoxy Nitrile Coupling

metal ion	bases (2 equiv)	products[a]
Na^+, K^+	$NaNH_2$, NaHMDS, NaO^{t}Bu, NaH, KHMDS, KO^{t}Bu	**3b/7b** only
Li^+	*n*-BuLi, LiHMDS, LDA	Major: **5b/8b**; Minor: **3b/7b**
Mg^{2+}	*i*-PrMgCl, NaHMDS/$MgBr_2$	**8b** only

[a] All reactions were carried out at −15 °C to room temperature in the presence of 2 equiv of bases in THF. Isolation of **5b** depends on the aging period. For further discussion on lithium's aggregates, see more in the text.

of the lithium alkoxide was slow and provided a mixture of **3b**, **7b**, and **8b**;[6] (3) the use of sodium or potassium bases gave *solely* cyclopropanes in 96% ee, which indicated that reaction was occurring via attack at C3 of epichlorohydrin because reaction at C1 would generate the opposite enantiomer via ***ent*-6b**.

Further studies revealed that the mode of addition played a pivotal role to achieve a clean cyclopropanation: the best conditions involved addition of 1.3 equiv of NaHMDS to a solution of **4b** and (+)-epichlorohydrin at −20 to −15 °C which afforded **3b**/**7b** (cis/trans = 85:15) in 95% assay yield (96% ee).[7] Surprisingly, utilizing similar conditions for **4a** (Ar = *p*-MePh**)** *provided the product **3a** in only 75% ee*. This striking result encouraged us to further explore the relationship between the nucleophilicity of arylacetonitrile anions and the regioselectivity (C1 vs C3 attack on epichlorohydrin) which is reflected in the er of **3** (Figure 1).

Focusing first on the effect of nucleophilicity on enantioselectivity, analysis of Figure 1 provides clear insight that the more basic carbanion reacts with epichlorohydrin less selectively[7b] (C1 vs C3 attack). This trend could reflect subtle electronic effects on hard/soft selectivity, ion-pairing effects, and/or changes in solvation of the carbanion with the shifting of electron density from the nitrile to the aromatic ring with more electron-withdrawing groups present. As further outlined below, this effect is a combination of a solvation/ion-pairing phenomenon and an electronic effect.

With lithium bases, chlorohydrin **5** is a discrete intermediate and conversion to epoxide **6** is slow (Table 1). In fact, *the Li−O bond in the aggregates*[8] *is sufficiently strong*[9] *that lithium alkoxide **5** is unreactive at −25 °C.*[7] Charging an additional equivalent of NaHMDS to the above reaction mixture led to cyclobutanes **8**/**9** (major) at <−15 °C, due to

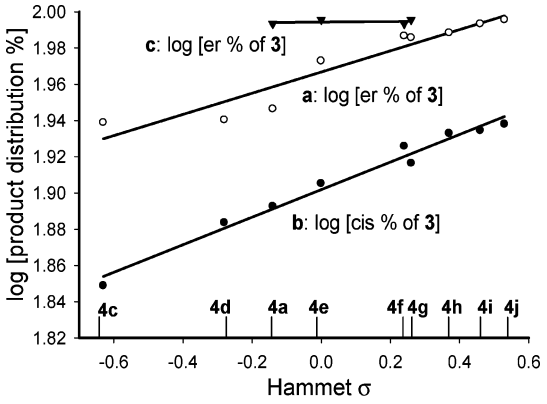
(5) For an example of magnesium halides as Lewis acids to open epoxide, see: Corbel, B.; Durst, T. *J. Org. Chem.* **1976**, *41*, 3648.

(6) For other examples of using lithium bases, also see: (a) Jeffery, J. E.; Kerrigan, F.; Miller, T. K.; Smith, G. J.; Tometzki, G. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2583. (b) Kusumoto, T.; Nakayama, A.; Sato, K.; Hiyama, T.; Takehara, S.; Osawa, M.; Nakamura, K. *Chem. Lett.* **1992**, 2047.

(7) (a) (+)-Epichlorohydrin was 98% ee. (b) See Supporting Information.

(8) For a recent review, see: Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. For leading references, see: (a) Reich, H. J.; Biddle, M. M.; Edmonston, R. J. *J. Org. Chem.* **2005**, *70*, 3375. (b) Carlier, P. R.; Lo, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 12819 and references therein.

(9) If the reaction mixture was quenched in aqueous MeCN, **5** was converted to **6** as promoted by OH^- generated from water quenching.



4	Ar	*cis* : *trans*	er (%), 3
c	4-Me_2NPh	2.4 : 1	86.0
d	4-MeOPh	3.3 : 1	86.3
a	4-MePh	3.6 : 1	87.5
e	Ph	4.1 : 1	93.0
f	4-ClPh	5.4 : 1	96.0
g	4-BrPh	4.7 : 1	95.8
h	3-ClPh	6 : 1	96.4
i	3-CF_3Ph	6.1 : 1	97.5
j	4-CF_3Ph	6.5 : 1	98.0

Figure 1. Substituent's effects on cyclopropanation.[7] *y*-axis = log[er % or cis %]. Reagents and conditions: (a/b) **4** → **3**, NaHMDS, THF, −15 °C. (c) **4** → **5** → **3** (vide infra), LiHMDS, *t*-BuOMe, −25 °C; NaHMDS, THF, −15 °C.

the M−O aggregation change. Alternatively, after removal of Li^+ through aqueous workup, the crude **5a** was exposed to NaHMDS/$(MeOCH_2)_2$/THF at −15 °C and afforded the desired **3a** with >97% ee (cis/trans = 85:15). This strategy was successfully applied to other substrates such as **4e**−**g** to obviate the substituent effects on the ee, generating the cyclopropanes **3e**−**g** in >97% ee (Figure 1, line c).[7] Therefore, *by changing the counterion, the erosion in ee is eliminated*, indicating that the original trend on nucleophilicity (Figure 1, line a), contributed from electronic effects, could be overridden by ion-pairing/solvation factors.

Line b in Figure 1 depicts the effect of carbanion nucleophilicity on the cis/trans ratio. A larger amount of the cis isomer is produced as the substituents become more electron-withdrawing. The cis/trans ratio is set in the S_Ni epoxide-opening step (**6b** to **3b**/**7b**) and is therefore decoupled from the factors which control the enantioselectivity. As outlined below, the cis/trans ratio is also affected by sterics, solvation, and ion pairing.

Ortho-substituted substrates were studied to probe the role of steric factors in controlling the cis/trans ratio. As shown in Figure 2, ortho substituents have a dramatic influence on the cis/trans selectivity as a result of steric hindrance as shown in the eclipsed conformations **A** and **B**. The solvated metal ion M occupies the position opposite to the ortho substituent Y to minimize steric interactions, which creates subsequent repulsion with the methylene in **A** and therefore reduces the energy difference with **B** to give lower cis/trans

	X,Y	*cis/trans*
4k	H,Cl	3.5 :1
4l	Cl, Cl,	1:1.1
4m	H, OMe	3.3:1

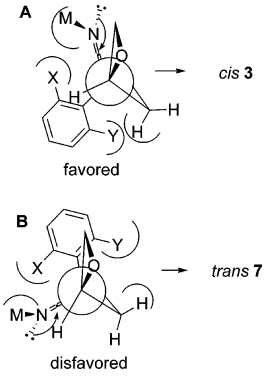
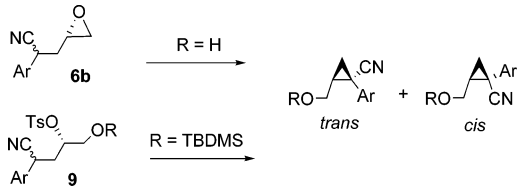


Figure 2. Ortho substituent's effects on cyclopropanation.[7] Reagents and conditions: **4** → **3/7**, NaHMDS, THF, −15 °C.

selectivity, as evidenced by **4k**,**l** vs **4f**,**h** (Figure 1).[7,8] However, for substrates **4m** vs **4c**, the unaffected cis/trans selectivity is believed to be due to the chelation between *o*-OMe and the metal ion.

In an attempt to isolate these parameters and further understand the selectivity of the intramolecular cyclopropanation, we next studied the isolated epoxide diastereomers **6b** and the tosylate **9** which bears a more bulky CH_2OTBS group. Subjecting **6b** and **9** to various bases and solvents,[7b] we found a turnover in selectivity depending on the solvent employed in the reaction (Table 2). The more significant

Table 2. Selected Data of Cyclopropanation of **6b** or **9**[7b]

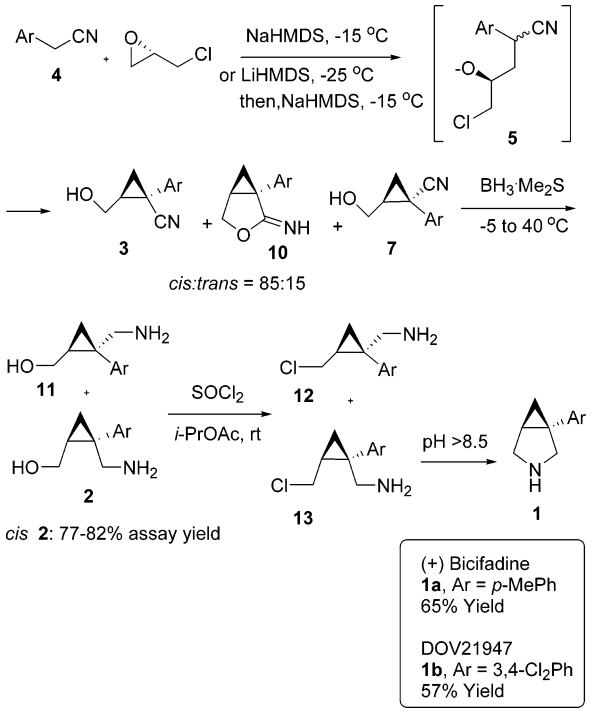


entry		Ar	base	solvent	cis/trans
1	**6b**	3,4-Cl_2Ph	KHMDS	PhMe	2.2:1
2	**6b**	3,4-Cl_2Ph	*t*-BuOK	THF/DMPU	4.3:1
3	**9a**	3,4-Cl_2Ph	KHMDS	PhMe	1:4.9
4	**9a**	3,4-Cl_2Ph	NaHMDS	THF	1.4:1
5	**9a**	3,4-Cl_2Ph	LiHMDS	THF	1.6:1
6	**9a**	3,4-Cl_2Ph	*t*-BuOK	THF/DMPU	7.3:1
7	**9b**	Ph	KHMDS	PhMe	1:5.7
8	**9b**	Ph	*t*-BuOK	THF/DMPU	9:1

effect on the selectivity on **9a**,**b** vs epoxide **6b** is consistent with the stereochemical analysis (Figure 2), as the aggregates are drastically affected by solvent polarity.[8]

We next returned our attention to the application of this methodology toward the synthesis of **1** (Scheme 3). Direct treatment of the crude cyclopropanation products with BH_3·Me_2S afforded a mixture of **2**/**11** in one pot. Efficient chlorination[7b] was achieved in almost quantitative yield by controlling the concentration of amino alcohol **2**/**11** free base

Scheme 3. Single-Stage Through Process



through slow subsurface addition to a solution of $SOCl_2$ in *i*-PrOAc at ambient temperature. The *cis*-chloride **13** was immediately cyclized to **1** upon adjusting the pH to >8.5. Thus, (+)-Bicifadine and DOV21947 HCl salt (>99% purity) were directly isolated in 65% and 57% overall yield, respectively, whereas **12** was rejected through crystallization.[7b]

In summary, we have developed an expedient, atom-economical, asymmetric synthesis of 1-aryl-3-azabicyclo-[3.1.0]hexanes in a single-stage through process *without isolation of any intermediates*. The counter metal ion, solvent, and substituents' effects on the epoxy nitrile coupling were further investigated, and cyclopropanes **3** were thus prepared in high ee and yield by controlling the reaction pathway through manipulating the nitrile anion aggregation state. Further mechanistic studies toward further understanding the aggregation effects on enantio- and diastereoselectivity are ongoing.

Acknowledgment. We gratefully acknowledge Drs. D. Hughes and K. Hansen (Merck & Co., Inc.) for helpful discussions.

Supporting Information Available: Experimental procedures/discussions including an alternative synthesis of DOV21947, characterization data, and methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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