Pergamon

Tetrahedron Letters 41 (2000) 8533–8537

TETRAHEDRON LETTERS

An unusual enhancement of chiral induction by chiral 2-imidazolidinone auxiliaries

Alaa A.-M. Abdel-Aziz, Junko Okuno, Shinsuke Tanaka, Tadao Ishizuka, Hirofumi Matsunaga and Takehisa Kunieda*

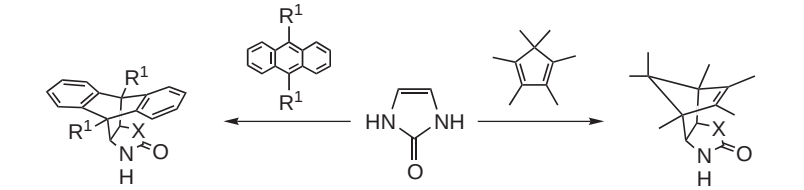
Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

Received 13 September 2000; accepted 14 September 2000

Abstract

Diastereoselectivity which is induced by the use of 2-imidazolidinone auxiliaries is greatly dependent on the *N*-substituents of the heterocycles, among which the bulky arenesulfonyl group is the moiety of choice. Reactions of this type afford an excellent level of diastereoselection in the methylation of *N*′-butyryl-2-imidazolidinones via the metal enolates. © 2000 Published by Elsevier Science Ltd.

Methodology which involves the use of heterocyclic chiral auxiliaries for a wide range of asymmetric transformations has been highly successful. Chiral 2-imidazolidinones,[1] as well as the widely used 2-oxazolidinone auxiliaries[2] hold considerable promise as chiral auxiliaries for use in diastereocontrolled reactions. Common methods for the preparation of 2-imidazolidinones are based on the reactions of 1,2-diamines with diethyl carbonate, phosgen, triphosgen or 1,1′-carbonyldiimide.[3] We recently reported an alternative route for the facile synthesis of sterically constrained tricyclic 2-imidazolidin-ones (**1**–**3**),[4] which served as versatile chiral auxiliaries. This approach involves the cycloaddition of 1,3-dihydro-2-imidazolone to the cyclic dienes such as anthracene and cyclopentadiene derivatives (Scheme 1).



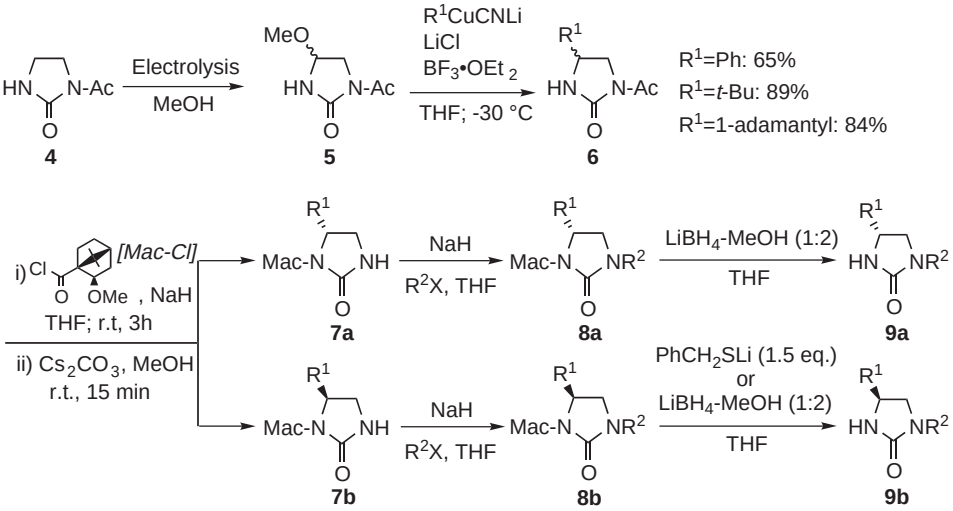
Scheme 1.

* Corresponding author. Fax: +81-96-362-7692; e-mail: tkuni@kumamoto-u.ac.jp

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01547-1

This paper describes a new synthetic route to optically active 4-*tert*-butyl and 4-(1-adamantyl)-2-imidazolidinones, which serve as highly potent chiral auxiliaries, from the parent 2-imidazolidinone heterocycle as well as a surprisingly strong chiral control effect by the *N*-substituents of such 2-imidazolidinone auxiliaries on diastereoselective enolate alkylations. The method involves the conversion of functionalized 4-methoxy and 4-phenylthio-2-imidazolidinones with organo cuprates to give the 4-alkyl- and 4-aryl-derivatives, followed by a facile optical resolution through either a stoichiometric or catalytic process.

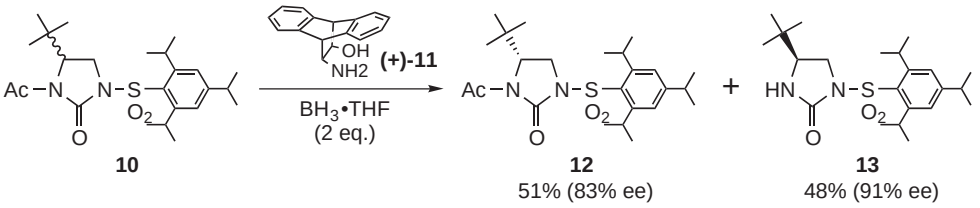
Thus, electrolytic oxidation[5] of *N*-acetyl-2-imidazolidinone (**4**) in methanol resulted in the exclusive formation of 4-methoxy-imidazolidinone (**5**), of which the methoxy groups were readily displaced with a variety of alkyl and aryl groups by using cuprate complexes in the presence of $BF_3{\cdot}OEt_2$. The 4-methoxy group was readily converted into the phenylthio group on treatment with benzenethiol/TFA. The latter nucleophilic substitution proceeded with or without the Lewis acid. Using this versatile procedure, 4-substituted 2-imidazolidinones (**6**) including bulky 4-*tert*-butyl and 4-(1-adamantyl) compounds were prepared in good yields (65–89%).[6] An optical resolution was performed with the aid of (1*S*,2*R*)-2-methoxy-1-apocamphanecarboxylic acid ((+)-Mac acid)[7] to give the diastereomeric *N*-Mac derivatives **7a** and **b**, which were readily separable by chromatography on silica gel (Scheme 2). The *N*′-protection with a series of arenesulfonyl chlorides with different degrees of bulkiness and methyl iodide, followed by removal of the Mac moieties either by reductive deacylation with $LiBH_4$/MeOH or by thiolysis with $PhCH_2SLi$ gave the enantiomerically pure 4-substituted-2-imidazolidinones **9a** and **b**.



Scheme 2.

The absolute configurations of the chiral 4-phenyl and 4-*tert*-butyl-2-imidazolidinones (**9b**) were determined by X-ray crystallographic analysis[8] of the *N*-Mac-isomers (**7b**).

An alternative means for optical resolution of the 2-imidazolidinones was provided by the dynamic kinetic resolution with enantioselective deacylation of the *N*-acetyl-derivatives via a catalytic process.[9] Thus, the *N*-acetyl-derivative **10** smoothly underwent an enantioselective partial deacetylation on treatment with borane (2 equiv.) in the presence of aminoalcohol (+)-**11** (0.1 equiv.) to give a quantitative yield of (4*R*)-**12** and (4*S*)-**13**, which were readily purified by a single recrystallization (Scheme 3).



Scheme 3.

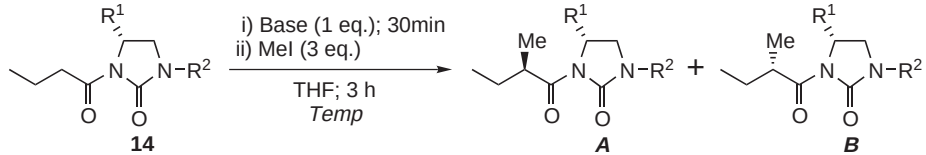
The chiral 2-imidazolidinone auxiliaries thus obtained could be conveniently evaluated by the sterically undemanding probe reaction, involving α-methylation of the butyryl derivatives (**14**), which is generally difficult to control with a high level of diastereoselection.[10] The diastereoselective methylations of the *N*-alkyl and *N*-arenesulfonyl-*N*′-butyryl-2-imidazolidinones (**14**) proceeded smoothly to give moderate to excellent diastereoselectivity when the reaction was performed with methyl iodide in the presence of lithium or sodium hexamethyldisilazanide (LHMDS or NHMDS) as well as lithium diisopropylamide (LDA).

As can be seen in Table 1, the chiral induction by the 2-imidazolidinone auxiliaries is greatly dependent on both the 4-substituent groups of the 2-imidazolidinones and the *N*-substituents which are located at a considerable distance from the site of the reaction. Apparently, a small structural variation in the chiral auxiliary may induce a tremendous effect on asymmetric control. It is noteworthy that the observed diastereoselectivity of the reaction was highly dependent on the bulkiness of the *N*-arenesulfonyl substituents on the 2-imidazolidinone auxiliaries, in which *ortho*-disubstituents played an important role in achieving an excellent level of diastereocontrol. The 2,4,6-triisopropylbenzenesulfonyl (Tps) and 2-mesitylenesulfonyl (Mes) groups represent the *N*-substituents of choice for the 2-imidazolidinone auxiliaries in regard to chiral induction and efficiency. Nevertheless, excellent diastereoselectivity was obtained with chiral 4-(1-adamantyl)-3-methyl-2-imidazolidinones as the auxiliary, providing, to our knowledge, the highest selectivity observed thus far. Such a positive effect by *N*-substituents was not apparent in the cases of 4-phenyl-2-imidazolidinones with considerably less steric hindrance. It is unlikely that the *N*′-substituents and metal species could significantly affect the *E*/*Z* ratio of enolates and the chelate structures which might play a crucial role in high level of chiral induction,[11] although we have no evidence at the present.

The *N*-substituent effect leading to a dramatic enhancement in chiral induction was also observed when sterically congested 2-imidazolidinone auxiliaries such as DHAIm (**1**), DMAIm (**2**) and HMCIm (**3**) were used in the diastereoselective methylation of *N*′-butyryl derivatives **15** using LHMDS as a base (Table 2). Our findings clearly show that the bulky *N*-sulfonyl substituents were much superior to alkyl groups, such as methyl and 2,4,6-trimethylbenzyl groups.

The present chiral auxiliaries are highly crystalline and could be recovered easily with $LiOH/H_2O_2$ in quantitative yields. In conclusion, this study demonstrates the remarkable diastereocontrolling effects of the *N*-substituents of 2-imidazolidinone auxiliaries, leading to excellent chiral auxiliaries, namely bulky *N*-(*ortho*-disubstituted benzenesulfonyl)-2-imidazolidinones. The mechanistic details for this reaction remain under investigation.

Table 1
The 1,4-disubstituent effect of 2-imidazolidinone auxiliaries on diastereocontrolled methylation

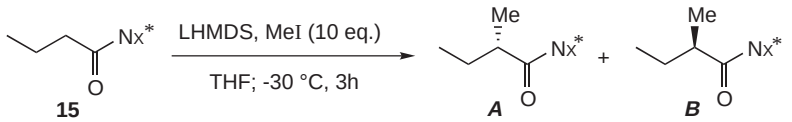


14 **A** **B**

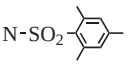
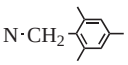
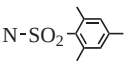
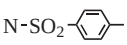
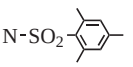
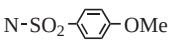
R^1	R^{2a}	Base	Temp. (°C)	Yield (%)[b]	*A*:*B*[c]	R^1	R^{2a}	Base	Temp. (°C)	Yield (%)[b]	*A*:*B*[c]
Ph	Tos	LHMDS	0	86 (88)	3.9:1	*t*-Bu	Me	LHMDS	−30	79 (91)	32:1
	Tps	LHMDS	0	75 (95)	5.7:1		Me	LDA	−30	86 (99)	37:1
	Me	LHMDS	0	89 (90)	5.2:1	1-Adamantyl	Tos	LHMDS	−30	54 (92)	38:1
t-Bu	Tos	LHMDS	−30	90 (98)	32:1		Mes	LHMDS	−10	66 (71)	179:1
	Mes	LHMDS	−10	65 (89)	190:1		Tps	LHMDS	−10	72 (72)	284:1
	Tps	LHMDS	−10	73 (82)	490:1		Me	LHMDS	−30	79 (92)	39:1
	Tps	LDA	−30	79 (100)	420:1		Me	LDA	−30	86 (86)	>500:1
	Tps	NaHMDS	−30	15 (21)[d]	17:1		Me	NaHMDS	−30	85 (85)	>500:1

[a] Tos: *p*-toluenesulfonyl; Mes: 2-mesitylenesulfonyl; Tps: 2,4,6-triisopropylbenzenesulfonyl.
[b] Determined by HPLC. Corrected yields in parentheses based on unchanged starting material.
[c] Determined by HPLC.
[d] Determined by ^{1}H NMR (500 MHz).

Table 2
The *N*-substituent effect of 2-imidazolidinone auxiliaries on diastereocontrolled methylation



15 A B

NX*H	R^2	LHMDS (equiv.)	Yield (%)[a]	*A*:*B*[b]	NX*H	R^2	LHMDS (equiv.)	Yield (%)[a]	*A*:*B*[b]
1	N-Me	2	97	1.8:1	**1**		2	84	31:1
1		2	97	4:1	**2**		2	82[c,d]	>500:1
1		2	82	9:1	**3**		5[e]	71[d]	>500:1
1		2	91	9:1					

[a] Isolated yields.
[b] Determined by HPLC.
[c] For 10 h.
[d] Determined by ^{1}H NMR (500 MHz) spectra.
[e] 31% yield was obtained by using 2 equiv. of LHMDS.

References

1. For recent examples, see: (a) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc*. **1997**, *119*, 6438–6439. (b) van Heerden, P. S.; Bezuidenhoubt, B. C. B.; Ferreira, D. *Tetrahedron Lett*. **1997**, *38*, 1821–1824.
2. For reviews, see: (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835–875. (c) *Idem*., *Aldrichim. Acta* **1997**, *30*, 3–12.
3. Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett*. **1998**, *39*, 9407–9410 and references cited therein.
4. Yokoyama, K.; Ishizuka, T.; Ohmachi, N.; Kunieda, T. *Tetrahedron Lett*. **1998**, *39*, 4847–4850.
5. Wang, P.-C. *Heterocycles* **1985**, *23*, 2237–2238.
6. Similarly, 4-*n*-butyl and 4-benzyl-2-imidazolidinones were prepared from 4-methoxy or 4-phenylthio derivatives in 61–78% yields.
7. Ishizuka, T.; Kimura, K.; Ishibuchi, S.; Kunieda, T. *Chem. Lett*. **1992**, 991–994.
8. X-Ray crystal data for **7b** (R^1 = phenyl) [mp 235°C (from hexane/CH_2Cl_2), $[\alpha]_D$ +56.1° ($CHCl_3$)]: orthorhombic, $P2_12_12_1$, a = 10.6487(6) Å, b = 20.1649(6) Å, c = 8.6086(6) Å, V = 1848.5(1) Å^3, Z = 4, μ = 6.66 cm^{-1}, R = 0.041. **7b** (R^1 = *tert*-butyl) [mp 192°C (from CH_2Cl_2/hexane), $[\alpha]_D$ −7.2° ($CHCl_3$)]: orthorhombic, $P2_12_12_1$, a = 12.833(1) Å, b = 13.234(1) Å, c = 10.8928(1) Å, V = 1849.9(2) Å^3, Z = 4, μ = 6.27 cm^{-1}, R = 0.035.
9. Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1998**, *39*, 6317–6320.
10. (a) Matsunaga, H.; Kimura, K.; Ishizuka, T.; Haratake, M.; Kunieda, T. *Tetrahedron Lett*. **1991**, *32*, 7715–7718. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 1184–1186.
11. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737–1739.