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# Asymmetric [4+3] Cycloadditions From Chiral α-Chloro Imines

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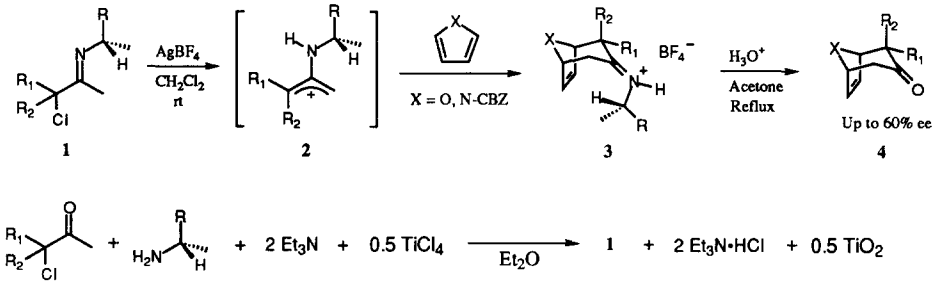
**Abstract:** The first asymmetric [4+3] cycloadditions of 2-aminoallyl cations derived from chiral α-chloro imines to furan and pyrrole systems are reported. The absolute configuration of the major enantiomer of the bicyclic ketone **4a** derived from the cycloadducts has been elucidated, and possible rationales for the observed stereoselectivity are discussed. © 1997 Elsevier Science Ltd.

Despite many known variants of heteroatom-substituted allyl cation mediated [4+3] cycloadditions,[1] asymmetric versions of this process have only recently been reported.[2] In search of a chiral auxiliary which could mediate such selectivity, we have found that chiral α-chloro imines (**1**, Scheme 1) could serve as efficient precursors to chiral 2-aminoallyl cations (**2**),[3] which are subsequently trapped by a furan or pyrrole in a facial and *endo* selective [4+3] fashion to give iminium salts (**3**). Mild hydrolysis cleaves the chiral amine auxiliary in such adducts to yield chiral bicyclo[3.2.1]octanone derivatives (**4**).

**Scheme 1.**

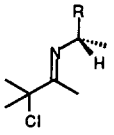
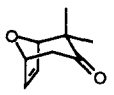
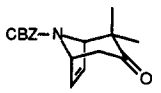
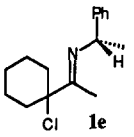
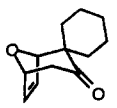
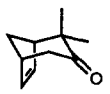
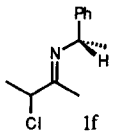
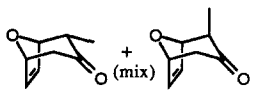
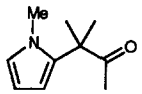
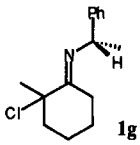
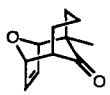



The sensitive α-chloro imines **1** were readily prepared from the corresponding α-chloro ketones and only 1.0 equivalent of the commercially available (*S*)-1-ethylamines using our modification[4] of De Kimpe's protocol (Scheme 1). The enantioselective [4+3] sequence was initiated by treatment of **1** with $AgBF_4$ (1 equiv.)[3] in $CH_2Cl_2$ at 22 °C under argon in the presence of excess furan or pyrrole, followed by acid hydrolysis (2*N* aq HCl-acetone, 1:1, reflux, 16 h).[5] The enantio-enriched cycloadduct ketones **4** were isolated; results are given in the Table.

From most of the chiral imines examined, moderate yields and enantiomeric excesses (ee) up to 60% were obtained. Consistent with a previous report by De Kimpe,[3] we found it was necessary to reflux the reaction mixture (ca. 40 °C) involving the alkyl imine **1a** (entry 1) to ensure a sufficient reaction rate. Surprisingly, imines from aromatic auxiliaries (e.g. **1b-1f**, entries 2-4, 7-9) gave smooth cycloadditions even at room

temperature. Imines having bulkier (**1c**, entry 3) and electron-poor (**1d**, entry 4) substituents gave both lower yields and ee's. Overall, the (*S*)-1-phenylethylamine derived imine **1b** (entry 2) gave the most favorable yields and ee's to **4a**.[6] The use of more polar solvents (e.g. $Et_2O$, THF, MeCN, $MeNO_2$) led to little or no cycloaddition. Neither reflux nor very low temperatures improved the yield or ee starting with **1b** (entry 2).

**Table. Summary of Enantioselective [4+3] Cycloaddition-Hydrolysis Results**[a]

| Entry | Imine (1) | Product (4) Isolated Yield (ee) (%) | Entry | Imine (1) | Product (4) Isolated Yield (ee) (%) |
|---|---|---|---|---|---|
| |  |  **4a** | 7 | **1b** R = Ph |  **4d** 23 (41)[c] |
| 1 | **1a** R = Cyclohexyl | **4a** 24 (40)[b] | 8 |  **1e** |  **4e** 13 (25)[c] |
| 2 | **1b** R = Ph | **4a** 37 (60)[b,c,d] | | | |
| 3 | **1c** R = Naphth | **4a** 17 (32)[b] | | | |
| 4 | **1d** R = 4-$NO_2$-Ph | **4a** 5 (6)[b] | | | |
| 5 | **1b** R = Ph |  **4b** 0 | 9 |  1f |  **4f** 16 (44)[b] **4g** 11 (0)[b] |
| 6 | **1b** R = Ph |  **4c** 36 | 10 |  **1g** |  **4h** 0 |

[a] See note 5 for experimental procedures; [b] determined by $^1H$ NMR with chiral shift reagent $Eu(tfc)_3$; [c] determined by HPLC using a Chiralcel OD column; [d] determined by chemical transformations and Mosher ester analysis, see text.

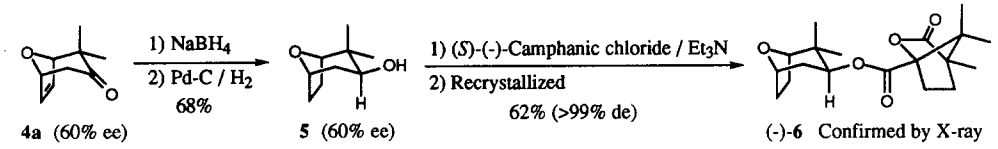
The scope of the applicable dienes has been briefly surveyed. Furan was frequently the best [4+3] trapping agent for these chiral aminoallyl cations (entries 1-4, 8-9). Neither 2-methylfuran nor cyclopentadiene (entry 5) gave cycloadducts. The electron-rich 1-methylpyrrole gave only the alkylated product **4c**[7] (entry 6). In the contrast, *N*-CBZ-pyrrole reacted analogous to furan, giving **4d** (entry 7).[8]

Structural variation on the chiral allyl cation precursor has led to the spiro-tricyclic product **4e**[9] (entry 8), but not to a doubly-bridged skeleton, as in **4h** (entry 10). A less stabilized cation intermediate (from **1f**, entry 9) was also productive, leading to the *optically active* equatorial adduct **4f** plus, interestingly, its *racemic* axial methyl epimer **4g** as an inseparable mixture.[10]

The absolute configuration of the major enantiomer (–)-**4a** was determined as depicted below (Scheme 2), and was assumed applicable to the analogous major cycloadducts **4** listed in the Table. Sequential hydride

reduction and hydrogenation of **4a** (60% ee, from entry 2) gave equatorial alcohol **5**[11] as the major product separable from its axial epimer. The (*R*)-MTPA Mosher ester from alcohol **5** gave an inseparable mixture of two diastereomers in a 4:1 ratio, and standard $^1$H NMR analysis[12] of them led to preliminary assignment of the absolute configurations of (–)-**5** and (–)-**4a** as drawn. Further X-ray single crystal structure determination of (–)-**6**,[13] the pure major diastereomeric camphanic ester from **5**, has unambiguously confirmed these assignments (Scheme 2).

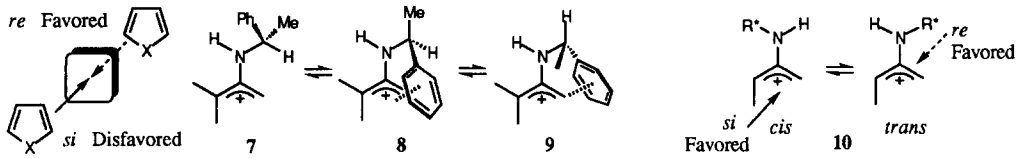
**Scheme 2.**




**4a** (60% ee) **5** (60% ee) (-)-**6** Confirmed by X-ray

A tentative hypothesis for the observed cycloaddition diastereoselectivity is suggested (Scheme 3). Rotamer **7**, the presumed energy minimum anticipated from computational studies on nucleophilic alkylations and 1,4- additions of related imines,[14] would explain the *re* facial preference of the diene approach, but not the big difference in reactivity between **1a** and **1b**, or **1b** and **1d**. This difference could be explained by additional π-stabilization from possible allyl cation–arene interactions, as illustrated in rotamers **8** and **9**. Consequently, dienes could attack preferentially from the less hindered *re* face of **8**, not the *si* face of **9**. The racemic axial cycloadduct **4g** might arise from the equally populated *cis* and *trans* isomers of the chiral aminoallyl cationic intermediate **10** (Scheme 3).

**Scheme 3.**




In conclusion, we have observed a novel route for certain enantioselective [4+3] cycloadditions based on chiral auxiliaries, and have elucidated the absolute steric course of such additions. Extensions and applications of this concept to related systems are under examination.

## References and Notes

1. Reviews of [4+3] cycloadditions include (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611; (b) Rigby, J. H.; Pigge, F. C. *Org. Reactions* (N.Y.), **1997**, in press.
2. (a) Lautens, M.; Aspiotis, R.; Colucci, J. *J. Am. Chem. Soc.* **1996**, *118*, 10930; (b) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.
3. De Kimpe, N.; Palamareva, M.; Verhe, R.; De Buyck, L.; Schamp, N. *J. Chem. Res. (S)* **1986**, 190. For an example of a 1-phthaloylamino-substituted oxyallyl species in a [4+3] cycloaddition, see Walters,

M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23.

4. De Kimpe, N.; Verhe, R.; De Buyck, L.; Moens, L.; Schamp, N. *Synthesis* **1982**, 43. We found it was more economic and workable to add 2-3 equiv. of $Et_3N$ as the HCl scavenger, and reduce the use of the chiral amine to only 1 equiv. All new chiral imines gave satisfactory IR, HRMS, $^1H$ and $^{13}C$ NMR data.
5. Representative procedure: to a stirred suspension of dry $AgBF_4$ (586 mg, 3.00 mmol) in $CH_2Cl_2$ (1 mL) was added a solution of **1b** (670 mg, 3.00 mmol) in furan-$CH_2Cl_2$ (1:1, 6 mL) at rt under Ar. The mixture was stirred in dark for 8-16 h, filtered through a Celite pad and the pad washed thoroughly with $CH_2Cl_2$. The combined filtrate was concentrated, the residue was dissolved in 2*N* aqueous HCl-acetone (1:1, 6 mL). The mixture was heated to reflux for 16 h, cooled to rt and extracted with ether, the combined extract was dried over $Na_2SO_4$, filtered, and concentrated. The residue was separated by silica gel chromatography (EtOAc-hexanes, 1:5) to give **4a** (168 mg, 1.11 mmol, 37%).
6. **4a**: $[\alpha]^{23}_D$ -62.4° (c 1.80, $CDCl_3$) (60% ee). Fohlisch, B.; Sendelbach, S.; Bauer, H. *Liebigs Ann. Chem.* **1987**, 1.
7. Turro, N. J.; Edelson, S. S.; Williams, J. R.; Darling, T. R.; Hammond, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 2283.
8. **4d**: an oil; $[\alpha]^{23}_D$ -24.0° (c 3.8, $CHCl_3$) (41% ee); IR (neat): 1704 $cm^{-1}$; $^1H$ NMR (65 °C, pyridine-$d_5$): δ 7.47 (d, J = 7.0 Hz, 2H), 7.36 (m, 2H), 7.30 (m, 1H), 6.29 (d, J = 5.0 Hz, 1H), 6.19 (d, J = 5.0 Hz, 1H), 5.32 (s, 2H), 5.03 (br s, 1H), 4.66 (br s, 1H), 2.85 (dd, J = 4.5, 16.5 Hz, 1H); 2.30 (d, J = 16.5 Hz, 1H), 1.20 (s, 3H), 1.04 (s, 3H); HRMS calcd for $C_{17}H_{19}NO_3$: 285.1370, found: 285.1365.
9. **4e**: $[\alpha]^{23}_D$ -2.8° (c 1.3, $CHCl_3$) (25% ee). Hoffmann, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899.
10. **4f+4g**: (ref. 7) $[\alpha]^{23}_D$ -2.1° (c 2.2, $CHCl_3$) (44% ee for **4f**, 0% ee for **4g**); $^{13}C$ NMR ($CDCl_3$): δ 209.7 (C), 207.0 (C), 135.4 (CH), 134.2 (CH), 134.1 (CH), 132.4 (CH), 82.6 (CH), 82.3 (CH), 78.7 (CH), 77.8 (CH), 52.1 (CH), 50.9 (CH), 46. 4 (C), 44.9 (C), 16.3 ($CH_3$), 10.6 ($CH_3$). The $^1H$ NMR methyl signals of **4f** (δ 1.00, equatorial) and **4g** (δ 1.35, axial) were assigned (Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940), and each was nicely resolved into two sets by the chiral shift reagent Eu(tfc)$_3$ and the corresponding ee was determined.
11. **5**: an oil; $[\alpha]^{23}_D$ -7.3° (c 2.2, $CHCl_3$) (60% ee); IR (neat): 3421 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.40 (m, 1H), 3.81 (d, J = 7.2 Hz, 1H), 3.60 (dd, J = 7.2, 10.8 Hz, 1H), 1.90-1.50 (m, 7H), 1.00 (s, 3H), 0.94 (s, 3H); $^{13}C$ NMR: δ 84.1 (CH), 75.0 (CH), 70.6 (CH), 40.3 (C), 38.1 ($CH_2$), 29.0 ($CH_2$), 24.9 $CH_2$), 23.6 ($CH_3$), 18.9 ($CH_3$); HRMS calcd for $C_9H_{16}O_2$: 156.1148, found: 156.1150.
12. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (b) Ohtani, I.; Kusumi, T.; Kashman, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092; (c) Ciavatta, M. L.; Trivellone, E.; Cimino, G. *Tetrahedron Lett.* **1994**, *35*, 7871. The $^1H$ NMR signals of the gem dimethyls of the major (3*S*, 2'*R*)-MTPA ester appear at δ 0.82 (axial) and 1.03 (equatorial), both upfield to those of the minor (3*R*, 2'*R*)-MTPA ester at δ 0.92 (axial) and 1.07 (equatorial).
13. (–)-**6**: mp 166-167 °C; $[\alpha]^{23}_D$ -6.3° (c 1.3, $CHCl_3$); IR ($CDCl_3$): 1783, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.97 (dd, J = 7.2, 9.0 Hz, 1H), 4.43 (m, 1H), 3.82 (d, J = 7.2 Hz, 1H), 2.41 (m, 1H), 2.30-1.62 (m, 10H), 1.13 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H); $^{13}C$ NMR: δ 173.3 (C), 162.3 (C), 86.3 (C), 79.0 (CH), 69.9 (CH), 69.4 (CH), 49.9 (C), 49.1 (C), 34.1 (C), 29.3 ($CH_2$), 25.7 ($CH_2$), 24.0 ($CH_2$), 23.6 ($CH_2$), 19.7 ($CH_2$), 18.6 ($CH_3$), 14.9 ($CH_3$), 12.0 ($CH_3$), 11.9 ($CH_3$), 4.86 ($CH_3$); HRMS calcd for $C_{19}H_{28}O_5$+$H^+$: 337.2016, found: 337.2020. Colorless crystal: $P2_12_12_1$ with a = 6.186(1), b = 14.001(3), c = 20.487(3) Å, Z = 4 and R = 2.9%; coordinates have been deposited with the Cambridge Crystallographic Data Center.
14. Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826 and references cited therein.

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