Pergamon

Tetrahedron Letters 42 (2001) 2541–2544

TETRAHEDRON LETTERS

Asymmetric Wittig reactions of chiral arsonium ylides. Part 2: Atroposelective olefination of axially chiral *N*,*N*-dialkyl 2-formyl-1-naphthamides

Wei-Min Dai* and Chi Wai Lau

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Received 8 December 2000; revised 15 January 2001; accepted 1 February 2001

Abstract—Atroposelective olefination of axially chiral *N*,*N*-dialkyl 2-formyl-1-naphthamides with chiral ligand-derived stable arsonium ylides proceeded in a kinetic resolution manner. The (*E*)-olefin products were obtained in excellent chemical yields and in up to 88:12 diastereoselectivity. Effects of the amide alkyl groups, metal counter ions and solvents on the diastereoselectivity were investigated.

Conformational isomers normally interconvert rapidly at room temperature and are difficult to separate as single entities. However, with increased steric congestion, the high rotational barrier about single bonds enables isolation of conformational isomers. Such a phenomenon arising from restricted rotation about a single bond is referred to as atropisomerism.[1] Classical examples are the biaryl atropisomers including derivatives of 1,1′-binaphthyl. Recently, non-biaryl atropisomers have attracted considerable attention in asymmetric reactions and catalysis.[2–6] We report here on the first atroposelective Wittig reactions of 2-formyl-1-naphthamides using chiral arsonium ylides.[7]

As illustrated in Fig. 1A, the enantiomers of axially chiral *N*,*N*-diisopropyl 2-formyl-1-naphthamide are in rapid equilibrium at room temperature. The rotational barrier measured at 2°C is 90.2 kJ/mol which corresponds to an estimated half-life of 12 minutes at 20°C.[8] We partially resolved this amide at 20°C by HPLC over a chiral stationary phase and the dynamic HPLC chromatogram is given in Fig. 1B.[9] As a consequence of the

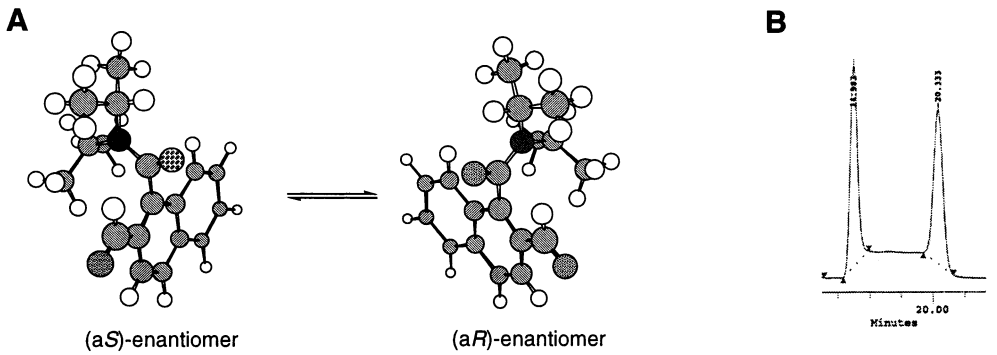


Figure 1. (**A**) Three-dimensional structures of *N*,*N*-diisopropyl 2-formyl-1-naphthamide. The *s-trans* conformation of the C2 formyl group is shown. (**B**) Dynamic HPLC chromatogram of the atropisomers shown in **A**, featuring a visible plateau between the peaks (performed over a Chiralpak AS column eluted with 95:5 hexane–isopropanol at 1.0 mL/min and by UV detection at 254 nm).

Keywords: arsenic and compounds; atropisomerism; olefination; Wittig reactions.

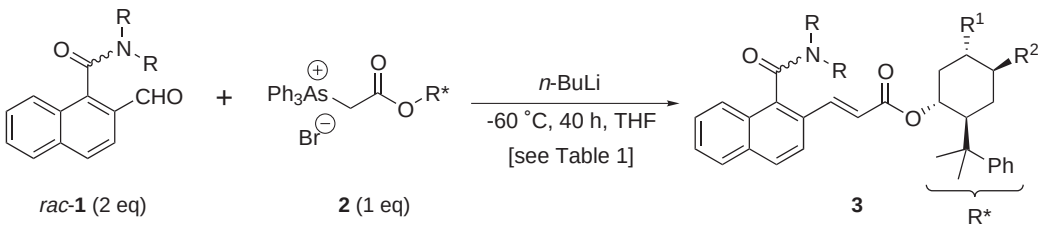
* Corresponding author. Fax: +852 2358 1594; e-mail: chdai@ust.hk

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00193-9

orthogonal relationship between the amide group and the naphthyl ring, the two faces of the formyl group at C2 are sterically well discriminated. It allows atroposelective nucleophilic addition with various organometallic reagents in chelation and non-chelation fashions.[6b,d] Dynamic resolution of 2-formyl-1-naphthamides has been reported using a chiral diamine as the resolving agent.[6f,g] As the continuation of our previous work on asymmetric Wittig reactions of 4-substituted cyclohexanones with chiral arsonium ylides,[7,10–12] we investigated the atroposelective olefination of four *N*,*N*-dialkyl 2-formyl-1-naphthamides *rac*-**1** with chiral arsonium salts **2**. The results are given in Scheme 1 and Table 1.[13]

The chiral arsonium salts **2**[7] were treated with *n*-BuLi at −60°C to form the corresponding arsonium ylides. The latter, without isolation, reacted with 2 equivalents[14] of the aldehydes *rac*-**1** at the same temperature for 40 h to furnish the (*E*)-olefins **3** in 84–98% yields, respectively. The excess aldehyde was recovered after the reaction in racemic form due to rapid equilibrium during the work-up and column chromatographic purification at 20°C. The diastereomeric ratio (dr) of each olefin product **3** was determined immediately after purification by ^{1}H NMR spectroscopy on a 400 MHz instrument (Table 1). For reactions of the (−)-8-phenylmenthol-derived arsonium ylide, the diastereoselectivity increases from 55:45 for the *N*,*N*-diethyl amide to 77:23 for the *N*,*N*-dicyclohexyl amide (entries 1–4). The same trend was observed for reactions of the arsonium ylide possessing the (1*R*,2*S*,4*R*)-(−)-4-(1-methylethyl)-2(1-methyl-1-phenylethyl)cyclohexanol moiety (entries 5–8). We noted that epimerization of **3** occurred slowly at 20°C. For example, a 77:23 mixture of **3** (entry 4) approached a 71:29 mixture after 21 h. Therefore, it is possible that the actual diastereomeric ratio of **3** should be slightly higher than the values listed in Table 1.

Next, we examined the effects of the metal counter ions, additives and solvents on the diastereoselectivity of reactions of the aldehyde *rac*-**1** (R = *c*-Hex) with the arsonium salt **2** derived from (−)-8-phenylmenthol (Scheme 2 and Table 2). We found that the metal counter ions influenced the reaction and the diastereoselectivity decreased in the following order: Li>Na>K ≈ Mg>Zn (entries 2–5 and 7). Addition of LiCl to the reaction had no effect, whereas $ZnCl_2$ and HMPA lowered the diastereoselectivity (entry 1 versus entries 6–8). Moreover, polar solvents gave better results than non-polar solvents such as toluene and dimethoxymethane (entries 9 and 10). The highest diastereomeric ratio of 88:12 was obtained in mixed THF–acetone (entry 12). These results may be interpreted by the chelation and non-chelation models[6b,d] in the addition step shown in Scheme 3. Because only (*E*)-olefins **3** were formed in the reaction, we can suggest that the (*Z*)-ylides[7] react favorably with either the metal-chelated aldehydes (a*R*)-**1** (related to the *s-cis*

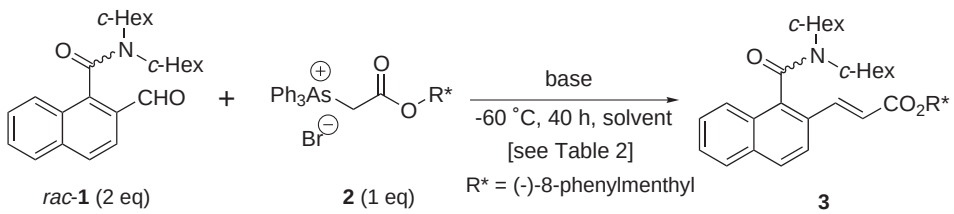


Scheme 1.

Table 1. Effects of *N*,*N*-dialkyl groups in amides **1** on diastereoselectivity of atroposelective olefination[a]

Entry	**1**, R	**2**, R*	**3** (%), dr[b]	Entry	**1**, R	**2**, R*	**3** (%), dr[b]
1	Et	R^1 = Me, R^2 = H	95, 55:45	5	Et	R^1 = H, R^2 = *i*-Pr	98, 56:44
2	*n*-Hex	R^1 = Me, R^2 = H	84, 62:38	6	*n*-Hex	R^1 = H, R^2 = *i*-Pr	84, 53:47
3	*i*-Pr	R^1 = Me, R^2 = H	97, 73:27	7	*i*-Pr	R^1 = H, R^2 = *i*-Pr	95, 74:26
4	*c*-Hex	R^1 = Me, R^2 = H	86, 77:23	8	*c*-Hex	R^1 = H, R^2 = *i*-Pr	91, 76:24

[a] The excess aldehyde **1** was recovered in racemic form due to a rapid racemization at room temperature.
[b] Determined by the integrations of the β olefinic protons in the ^{1}H NMR spectra recorded on a 400 MHz instrument.



Scheme 2.

Table 2. Effects of metal counter ions, additives, and solvents on diastereoselectivity of olefin **3**[a]

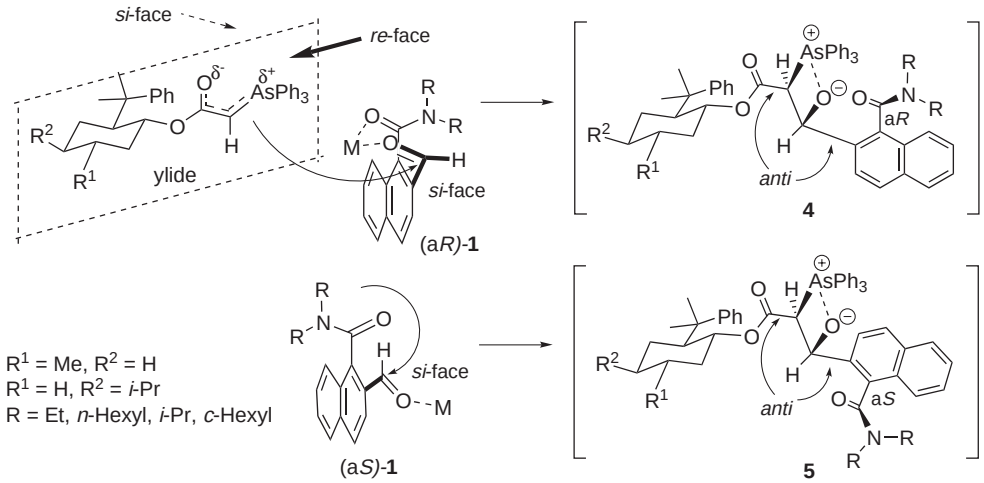
Entry	Reaction conditions	**3** (%), dr[b]	Entry	Reaction conditions	**3** (%), dr[b]
1	*n*-BuLi, THF	86, 77:23	9	*n*-BuLi, THF–toluene (5:2)	82, 71:29
2	$(TMS)_2NLi$, THF	96, 70:30	10	*n*-BuLi, THF–$CH_2(OCH_3)_2$ (1:1)	90, 65:35
3	$(TMS)_2NNa$, THF	92, 66:34	11	*n*-BuLi, THF–acetone (1:1)[c]	84, 81:19
4	$(TMS)_2NK$, THF	94, 61:39	12	*n*-BuLi, THF–acetone (1:1)[c,d]	93, 88:12
5	EtMgCl, THF	74, 62:38	13	*n*-BuLi, THF–EtOH (1:1)	86, 76:24
6	*n*-BuLi, LiCl (5 equiv.), THF	91, 77:23	14	*n*-BuLi, THF–DMF (1:1)	77, 73:27
7	*n*-BuLi, $ZnCl_2$ (2 equiv.), THF	78, 56:44	15	*n*-BuLi, THF–CH_3CN (1:1)	85, 78:22
8	*n*-BuLi, HMPA (2.5 equiv.), THF	92, 62:38			

[a] Deprotonation of **2** with *n*-BuLi or other bases was carried out first in THF followed by addition of the additive, or another solvent. After stirring the mixture at −60°C for 30 min, the aldehyde *rac*-**1** was added. After the reaction, the excess aldehyde was recovered in racemic form due to a rapid racemization at room temperature.

[b] Determined by the integrations of the β olefinic proton in the ^1H NMR spectrum recorded on a 400 MHz instrument.

[c] Aldol by-product formed from aldehyde *rac*-**1** and acetone was obtained.

[d] Three equivalents of aldehyde *rac*-**1** were used.



Scheme 3.

conformation of the C2 formyl group) or the metal-coordinated aldehydes (a*S*)-**1** (similar to the *s-trans* conformation of the C2 formyl group). The other two possible pathways leading to (*Z*)-olefins are not considered here. Formation of the diastereomeric (*E*)-**3** may involve betaine intermediates. As a simple 'working hypothesis', we consider that addition of the ylides with the aldehydes arrives directly at the four-membered ring intermediates **4** and **5** followed by the *syn* elimination of $Ph_3As{=}O$ in the decomposition step to the alkenes (not shown).[7,15] In the case of non-chelation control (M = Li, polar solvent), the Li-coordinated aldehydes (a*S*)-**1** react predominately with the ylides to give (*E*)-**3** possessing an axial *S* chirality. On the other hand, the metal-chelated aldehydes (a*R*)-**1** (M = Mg, Zn) react with the ylides to produce (*E*)-**3** possessing an axial *R* chirality. Therefore, it results in diminished diastereoselectivity when the reaction conditions promote metal chelation. In the presence of HMPA, the metal-free *s-cis* conformation of (a*R*)-**1** and the metal-free *s-trans* conformation of (a*S*)-**1** contribute to the olefination in favor of the latter aldehyde. The steric difference among the two intermediates **4** and **5** makes **5** much more stable because the amide moiety in **4** is close to the bulky triphenylarsine group. The same major diastereomer in all runs listed in Table 2 was experimentally confirmed. We assume that it should possess an axial *S* chirality formed through the intermediate **5**.

In summary, we have examined the first atroposelective Wittig reactions of axially chiral 2-formyl-1-naphthamides with arsonium ylides possessing the menthol-based chiral ligands. The olefination can be carried out at low temperature (−60°C) to give the (*E*)-olefins in excellent chemical yields and in up to 88:12 diastereomeric ratio. A reaction mechanism was proposed to account for the effects of metal counter ions, additives and solvents on diastereoselectivity. Due to the instability of the axial chirality at room temperature, the absolute stereochemistry of the major isomers of **3** has not been determined. Further research toward this goal is underway in our laboratory.

Acknowledgements

We thank the Department of Chemistry, HKUST and the Research Grants Council of the Hong Kong Special Administrative Region, China (HKUST6068/98P) for financial support.

References

1. (a) Oki, M. In *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1983; Vol. 14, pp. 1–81; (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp. 1142–1155.
2. Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.
3. Selected examples of axially chiral anilides, see: (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (b) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955. (c) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012. (d) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607. (e) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967. (f) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295. (g) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 2634. (h) Kitagawa, O.; Momose, S.; Fushimi, Y.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 8827. (i) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108. (j) Bach, T.; Schröder, J.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 9003. (k) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907.
4. Selected examples of axially chiral *N*-phenylimides, see: (a) Curran, D. P.; Geib, S.; DeMello, N. *Tetrahedron* **1999**, *55*, 5681. (b) Kondo, K.; Fujita, H.; Suzuki, T.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 5577. Also see Refs. 3a,g.
5. Selected examples of axially chiral benzamides, see: (a) Koide, H.; Uemura, M. *Chem. Commun.* **1998**, 2483. (b) Koide, H.; Uemura, M. *Tetrahedron Lett.* **1999**, *40*, 3443. (c) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875. (d) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033.
6. Selected examples of axially chiral 1-naphthamides, see: (a) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899. (b) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577. (c) Clayden, J. *Synlett* **1998**, 810 and references cited therein. (d) Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363. (e) Clayden, J.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1379. (f) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2556. (g) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279.
7. Dai, W.-M.; Wu, J.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979.
8. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
9. (a) Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2069; also see: (b) Schurig, V.; Keller, F.; Reich, S.; Fluck, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3475.
10. Recent reviews on asymmetric olefination, see: (a) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. (b) Li, A.-H.; Dai, L.-X. *Chem. Rev.* **1997**, *97*, 2341. (c) Tanaka, K.; Fuji, K. *J. Syn. Org. Chem. Jpn.* **1998**, *56*, 521.
11. Asymmetric Horner–Wadsworth–Emmons reactions using chiral phosphorous reagents, see: (a) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284 and references cited therein. (b) Norrby, P.-O.; Brandt, P.; Rein, T. *J. Org. Chem.* **1999**, *64*, 5845. (c) Pedersen, T. M.; Jensen, J. F.; Humble, R. E.; Rein, T.; Tanner, D.; Bodmann, K.; Reiser, O. *Org. Lett.* **2000**, *2*, 535. (d) Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611. (e) Tanaka, K.; Watanabe, T.; Shimamoto, K.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599.
12. Enantioselective Wittig–Horner and Horner–Wadsworth–Emmons reactions using external chiral reagents, see: (a) Toda, F.; Akai, H. *J. Org. Chem.* **1990**, *55*, 3446. (b) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753. (c) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 515. (d) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997.
13. All new compounds are fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and HRMS.
14. Dynamic kinetic resolution of aldehyde *rac*-**1** is an interesting and attractive aspect. However, in a reaction using 1 equivalent of aldehyde *rac*-**1** (R = *c*-Hex) at −60°C for 40 h, the olefin **3** was obtained in 65:35 diastereomeric ratio and in 84% yield at 84% conversion of the aldehyde. It corresponds to a 52.5:47.5 ratio of selectivity among the enantiomers of the aldehyde if one assumes that the remaining 16% aldehyde is optically pure.
15. Lloyd, D.; Gosney, I. In *The Chemistry of Arsenic, Antimony and Bismuth Compounds*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1994; pp. 669–670.