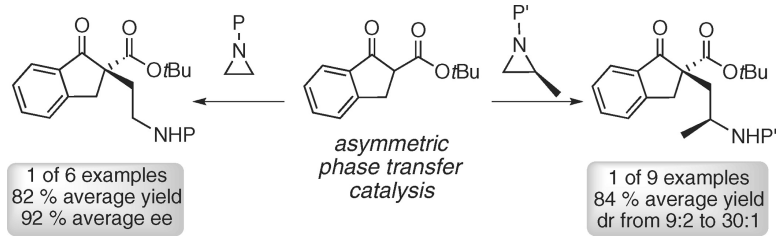
Communication

Enantio- and Diastereoselective Catalytic Alkylation Reactions with Aziridines

Thomas A. Moss, David R. Fenwick, and Darren J. Dixon

J. Am. Chem. Soc., **2008**, 130 (31), 10076-10077 • DOI: 10.1021/ja8036965 • Publication Date (Web): 11 July 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 07/11/2008

Enantio- and Diastereoselective Catalytic Alkylation Reactions with Aziridines

Thomas A. Moss,[†] David R. Fenwick,[‡] and Darren J. Dixon*,[†]

School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, U.K., and Pfizer Global Research & Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, U.K.

Received May 18, 2008; E-mail: darren.dixon@man.ac.uk

The enantioselective construction of γ-amino butyric acid derivatives from simple starting materials via asymmetric catalysis provides convenient access to a range of structurally diverse natural products, pharmaceutical compounds, and potential building blocks for γ-peptides and foldamer chemistry. To this end, developments in the field of enantioselective Michael additions of carbonyl compounds to nitroolefins have been significant with highly enantioselective examples known to both nitroethylene and β-substituted nitroolefins.[1,2]

We recognized a complementary, synthetically powerful and as yet unreported route to these compounds could involve a catalytic enantioselective alkylation reaction of a carbon acid with a protected amino ethylene synthon,[3] such as an *N*-protected aziridine.[4] Furthermore, such a reaction would install directly a protected amino group and allow γ-substituents to be incorporated into the produced γ-amino acid backbone. Attracted by the simplicity of the approach and the synthetic potential of the methodology, we began our investigations.

Herein we report a direct enantioselective catalytic alkylation reaction of methine pronucleophiles (Scheme 1) with *N*-sulfonyl aziridines leading to products containing the amino ethylene group attached to a stereogenic quaternary carbon ($R^1R^2R^3CCH_2CH_2NHP$) in high enantiomeric excess. Extension of the work to include diastereoselective variants is also described.

Preliminary studies using *tert*-butyl indanone carboxylate **1a** as a representative pronucleophile and *N*-mesitylene sulfonyl aziridine[5] **2a** were performed (Table 1). Initially, bifunctional cinchona catalysts **4a** and **b** (entries 1 and 2) were screened for activity in dichloromethane as solvent. At room temperature, the reaction was prohibitively slow (15 and 10% conversion after 48 h), giving the alkylation adduct in low enantioselectivity (10 and 6%, respectively), leading us to conclude that *N*-sulfonyl protected aziridines were unsuitable electrophiles for these bifunctional organocatalysts. To address the need for enhanced reactivity, we screened various phase transfer catalysts (**4c**−**f**) and base combinations.[6−8] Phase transfer catalysis has previously been employed in conjunction with the phosphorine base, BEMP.[9] Accordingly, in an initial proof of concept, we found indanone adduct **3a** was afforded in an encouraging 33% ee when 10 mol % of phase transfer catalyst **4f**[10] was employed with 10 mol % of BEMP (entry 3). Anticipating a prevalent background reaction would operate under these conditions,[5] we turned to a 50% aqueous solution of Cs_2CO_3 as the base. Gratifyingly, the alkylation adduct was formed in 91% ee, although the reaction was slow (35% conversion after 48 h, entry 4). A versatile feature of aziridine chemistry is that the reactivity of the electrophile can be tuned by judicious choice of nitrogen protecting group. By using *o*-(trifluoromethane)benzenesulfonyl aziridine **2b** instead of **2a**, a significant enhancement in reactivity was realized; complete conversion to the alkylation product was observed after 48 h at 0 °C (94% ee, entry 8). After screening various cinchona alkaloid derived phase transfer catalysts (**4c**−**f**, entries 5−8), we found **4f** bearing the bulky adamantoyl ester was the most selective.[10] By cooling the reaction mixture to −20 °C, a small increment in selectivity was observed (95% ee, entry 9), which was further enhanced by using a milder 50% aqueous K_2HPO_4 mixture as the base, furnishing the alkylation product in an impressive 97% ee (entry 10, Table 1).

Scheme 1. Enantio- and Diastereoselective Aziridine Alkylation Pathways

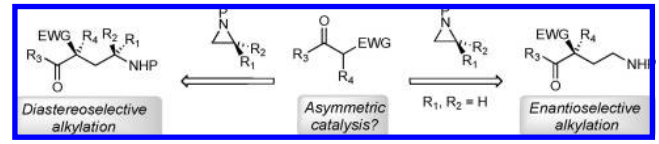
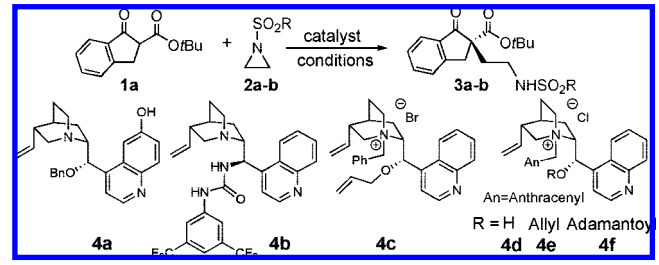


Table 1. Preliminary Studies into the Enantioselective Alkylation of *tert*-Butyl Indanone Carboxylate **1a** with Aziridine Electrophiles



entry	R	catalyst	conditions[a]	conv[b] 48 h	ee[c] %
1	Mes	**4a**	rt, CH_2Cl_2	15	10
2	Mes	**4b**	rt, CH_2Cl_2	10	6
3	Mes	**4f**	BEMP (10%), rt	100	33
4	Mes	**4f**	50% aq Cs_2CO_3, rt	35	91
5	*o*-$CF_3C_6H_4$	**4c**	50% aq Cs_2CO_3, 0 °C	100	24
6	*o*-$CF_3C_6H_4$	**4d**	50% aq Cs_2CO_3, 0 °C	80	21
7	*o*-$CF_3C_6H_4$	**4e**	50% aq Cs_2CO_3, 0 °C	100	51
8	*o*-$CF_3C_6H_4$	**4f**	50% aq Cs_2CO_3, 0 °C	100	94
9	*o*-$CF_3C_6H_4$	**4f**	50% aq Cs_2CO_3, −20 °C	100	95
10	*o*-CF_3C_6H	**4f**	50% aq K_2HPO_4, −20 °C	100[d]	97

[a] For entries 3−10, reactions were performed in a 0.1 M solution of 9:1 toluene:$CHCl_3$. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis. [d] Conversion after 72 h.

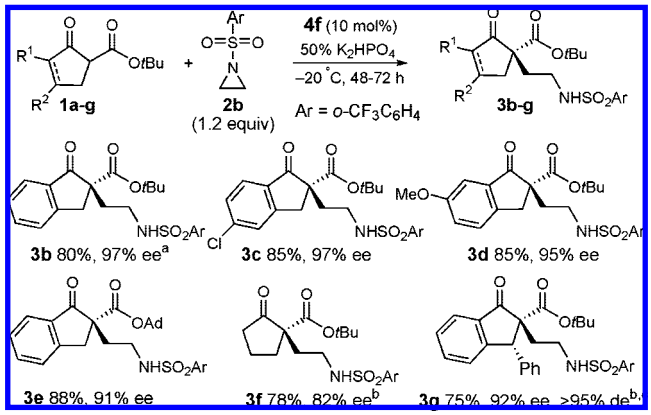
With optimal conditions established, the scope of the reaction was then probed. High enantioselectivities were observed for a range of substituted indanone pronucleophiles bearing bulky ester substituents (91−97% ee, **3b**−**e**). Using the more basic Cs_2CO_3 (aq), *tert*-butyl cyclopentanone carboxylate was also found to be a good substrate leading to the alkylated product in high yield and enantiomeric excess (82% ee). In an extension of this methodology, effective molecular recognition was witnessed when a pronucleophile bearing an additional stereocenter was employed. Thus with an excess of racemic *tert*-butyl 3-phenylindanone-2-carboxylate, efficient production of **3g** in high enantioselectivity (92% ee) and as a single diastereoisomer was observed (Chart 1).

To extend the utility of the reaction, we wished to incorporate enantiopure chiral aziridines. As regioselective ring opening usually occurs on the less hindered carbon of the aziridine, this would allow product substitution patterns to be obtained which would not normally be accessible by the commonly employed β-substituted nitroolefin Michael reactions. In an initial proof of concept, indanone **1a** was treated with *N*-nosyl

[†] The University of Manchester.
[‡] Pfizer Global Research & Development.

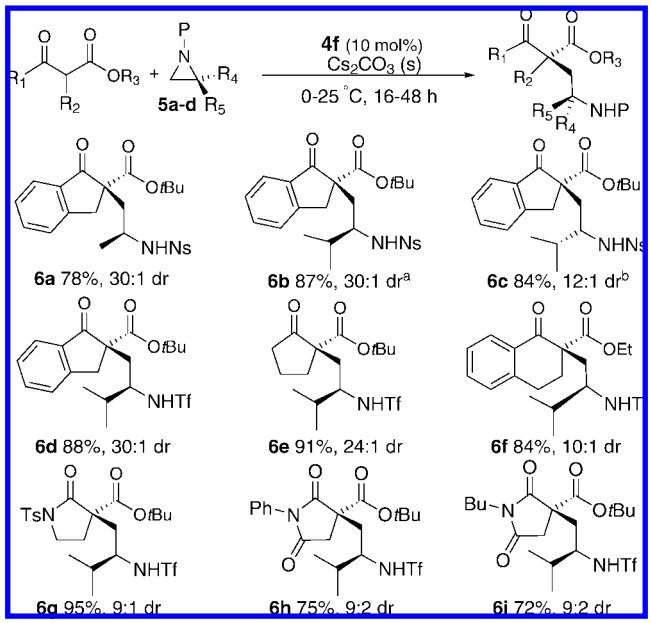
10.1021/ja8036965 CCC: $40.75

Chart 1. Enantioselective Ring Opening of Unsubstituted Aziridines with Phase Transfer Catalyst **4f**



[a] For desulfonation of **3b**, see Supporting Information. [b] Reaction performed at 0 °C with 50% aq Cs_2CO_3 as the base. [c] Relative stereochemical configuration assigned by analogy.[11]

Chart 2. Diastereoselective Ring Opening of Chiral Aziridines **5a**−**d** with Phase Transfer Catalyst **4f**

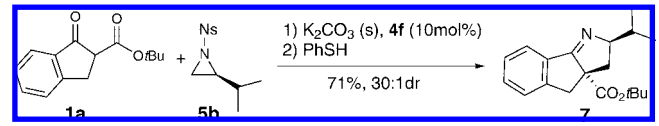


[a] The dr = 2:1 when **4f** was replaced with TBAB (10 mol %). [b] Relative and absolute stereochemical configurations were determined by X-ray analysis.

aziridines bearing both small (**5a**, R_4 = H, R_5 = Me) and bulky (**5b**, R_4 = H, R_5 = ^{i}Pr; **5c**, R_4 = ^{i}Pr, R_5 = H) substituents, with 10 mol % of phase transfer catalyst **4f** in the presence of solid cesium carbonate[12] (Chart 2).

Pleasingly, it was possible to obtain the *matched* enantiopure alkylation products (**6a** and **6b**) in high yields and high stereocontrol. In the *mismatched* case, catalyst control overrode the weak natural substrate control and **6c** was afforded in good diastereomeric excess (12:1 dr). Nosyl substituted aziridine **5b** was found to react slowly with non-indanone-based pronucleophiles. However, reactivity was greatly enhanced when the corresponding *N*-trifluoromethanesulfonyl protected aziridine[13] (**5d**) was employed with a range of pronucleophiles including indanones (**6d**), cyclopentanones (**6e**), tetralones (**6f**) lactams (**6g**), and succinimides (**6h**, **6i**), giving the products in high yields and in moderate to high diastereomeric ratios (9:2 to 30:1 dr).[14]

Scheme 2. One-Pot Alkylation/Desulfonation/Cyclization Sequence



As *N*-nosyl substituted sulfonamides are readily cleaved with thiols in the presence of K_2CO_3(s),[15] a one-pot alkylation/deprotection sequence appeared feasible via a modification of the established conditions. Pleasingly, with K_2CO_3(s) as the base and a staged addition of thiophenol, tricyclic indanone imine **7**, a product of intramolecular condensation, was formed in good yield and high diastereomeric excess (Scheme 2).

In conclusion, we have developed the first highly enantioselective aziridine alkylation reaction under phase transfer catalysis. Using single enantiomer aziridines, moderate to high catalyst controlled diastereoselectivities can be observed. Using a *N*-nosyl protected aziridine allowed a one-pot alkylation/desulfonation/cyclization sequence to diastereomerically pure tricycle **7**. Work to exploit this methodology in total synthesis is currently underway and will be reported in due course.

Acknowledgment. We gratefully acknowledge the EPSRC and Pfizer Global Research and Development (to T.A.M.). D.J.D. would like to thank Aurelie Alba for preliminary studies in this project.

Supporting Information Available: Experimental procedures and spectral data for compounds **2a**,**b**, **3a**−**g**, **4f**, **6a**−**i**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (b) Santanu, M.; Yang, J.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (d) Takemoto, Y.; Miyabe, H. *Chimia* **2007**, *61*, 269.
(2) For recent examples of secondary amine catalyzed Michael additions of aldehydes to nitroolefins, see: (a) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608. (b) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610. (c) Garcia-Garcia, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (d) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, 4722.
(3) For early studies using β-haloamines as electrophiles in β-ketoester alkylations, see: Barltrop, J. A. *J. Chem. Soc.* **1947**, 399.
(4) For reviews on ring opening of aziridines, including asymmetric methods, see: (a) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
(5) For a base-catalyzed process, see: Moss, T. A.; Alba, A.; Hepworth, D.; Dixon, D. J. *Chem Commun.* **2008**, *21*, 2474 and references cited therein.
(6) (a) Blyumin, E. V.; Gallon, H. J.; Yudin, A. K. *Org. Lett.* **2007**, *9*, 4677.
(7) For reviews on PTC, see: (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.
(8) For selected examples of advances in asymmetric phase transfer catalysis, see: (a) O'Donnell, M. J.; Bennet, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (c) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (d) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (e) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (f) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461. (g) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790.
(9) (a) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775. (b) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *Org. Lett.* **2005**, *7*, 3207.
(10) (a) Bernardi, L.; Lopez-Cantarero, J.; Neiss, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772. For early studies, see: (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.
(11) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, *22*, 2284.
(12) For alkylations with chiral aziridines **5a**−**c**, Cs_2CO_3 (s) or Cs_2CO_3 (aq) as the base was found to be superior to the milder K_2HPO_4 (aq), whereas with **5d** Cs_2CO_3(s) was found to be optimal.
(13) For deprotection procedures, see: *Protective Groups in Organic Synthesis*; Wuts, P. G. M., Greene, T. W., Eds.; Wiley: New York, 2007.
(14) Using **4f** and Cs_2CO_3(s), good reactivity but poor diastereomeric ratios were observed with a range of noncyclic phenyl cyanoacetate nucleophiles.
(15) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

JA8036965