

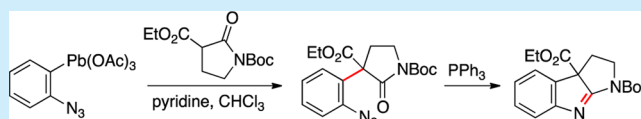
Efficient Synthesis of 3H-Indoles Enabled by the Lead-Mediated α -Arylation of β -Ketoesters or γ -Lactams Using Aryl Azides

Fei Zhou and Tom G. Driver*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, United States

S Supporting Information

ABSTRACT: The development of a lead-mediated α -arylation reaction between aryl azides and β -ketoesters or γ -lactams that facilitates the formation of 3H-indoles is disclosed. Twenty-five examples are included which demonstrate the generality of this reaction to access aryl azides bearing tetrasubstituted *o*-alkyl substituents. When paired with a Staudinger reduction, this reaction streamlines the synthesis of functionalized 3H-indoles.



The development of new efficient processes to construct *N*-heterocycles continues to motivate synthetic groups because of the ubiquitous nature of these structural motifs in bioactive and electronic molecules.^{1,2} Our group believes that these important compounds could be efficiently synthesized through transition-metal-catalyzed C–H bond amination, which would create the ArN–C bond from aryl azides. While we have successfully developed a series of C–H bond amination processes,^{3–5} the number of steps often required to access the aryl azide substrates diminished the overall efficiency of our *N*-heterocycle synthesis. In our intramolecular sp²–C–H bond amination studies,^{5b} seven linear steps were required to introduce the fully substituted *o*-alkyl substituent present in the aryl azide (e.g., **1**) (Scheme 1). This study underscored the need to streamline our substrate construction,⁶ and we anticipated that a modular synthesis could be achieved if the aryl azide moiety was installed through an α -arylation of a carbonyl compound.^{7–12} We were surprised, however, to find that no examples of this reaction existed with aryl azides.¹³ Herein, we report the first α -arylation of β -ketoesters and γ -lactams with aryl azides and leverage this reaction to efficiently synthesize 3H-indoles.

While there are many catalyzed and uncatalyzed α -arylation reactions of carbonyl compounds,^{7–13} our survey of popular methods and environmentally benign arylating reagents found

Scheme 1. Current Challenges To Synthesizing 2-Substituted Aryl Azides

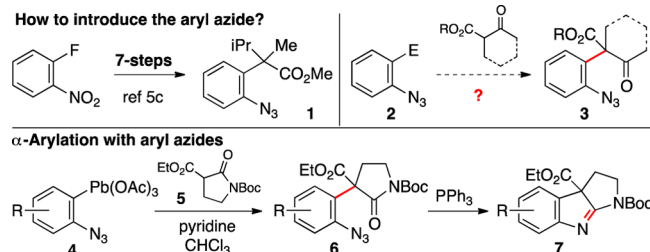


Table 1. Determination of the Optimal Conditions for α -Arylation

entry	base (equiv)	4a (equiv)	9a (equiv)	yield ^a (%)
1	none	1	5	90
2	none	1	3	89
3	none	1	1.05	59
4	dabco (3)	1	1.05	44
5	phenanthraline (3)	1	1.05	62
6	pyridine (3)	1	1.05	78
7	pyridine (3)	1	1.05	87 ^b
8	pyridine (3)	1.05	1	83 ^b
9	pyridine (3)	3	1	88 ^b
10	pyridine (3)	1	1.05	45 ^c

^aAs determined using ¹H NMR spectroscopy using CH₂Br₂ as an internal standard. ^bReaction performed at 50 °C. ^cTwo-step yield from **8a**.

them to be incompatible with the *o*-azide moiety.¹⁴ The failure of these methods prompted us to examine the α -arylation of β -ketoesters using an aryllead as the electrophilic reagent. Although the use of these complexes is well-established,¹¹ there are no examples of using an aryl azide substituent (much less an *o*-azide) in the α -arylation processes. The requisite 2-azidoarylboronic acid pinacol ester (**8**)¹⁵ or analogous stannane using the conditions reported by Pinhey and co-workers without any decomposition of the azido group.^{11b,c} With **4a** in hand, a variety of conditions were screened to find the optimal conditions for the α -arylation of β -ketoester **9a**

Received: April 11, 2014

Published: May 27, 2014

Table 2. Effect of Changing the Identity of the β -Ketoester

entry ^a	#	β -ketoester 9	aryl azide 6	%, yield ^b
1	b			89
2	c			97
3	d			97
4	e			79
5	f			75
6	g			53
7	h			86
8	i			79
9	j			79 d.r. 91:9
10	k			63 d.r. 91:9
11	l			89
12	m			54 d.r. 50:50
13	n			n.r.

^aReaction performed using 1 equiv of **4a**, 1.05 equiv of **9**, and 3 equiv of pyridine in CHCl_3 at 50 °C. ^bIsolated yield of **6** after silica gel chromatography; only product obtained.

(Table 1). For the initial screen, an excess of **9a** was used (entries 1–3). We found that the equivalents of **9a** could be reduced to three without attenuating the yield of **6a**. A significant reduction in conversion was observed, however, when a slight excess of the β -ketoester was used (entry 3). To improve the conversion, several amine bases were screened

Table 3. Determination of the Optimal Conditions for α -Arylation

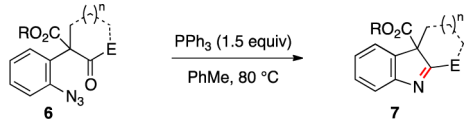
entry ^a	4	R ¹	R ²	9	6	%, yield 6 ^b
1	b	F	H	a	o	67
2	c	Cl	H	a	p	67
3	d	Me	H	a	q	77
4	e	H	OMe	a	r	94
5	f	H	Me	a	s	94
6	g	H	F	a	t	58 ^c
7	h				u	67
8	b	F	H	i	v	75
9	c	Cl	H	i	w	56
10	d	Me	H	i	x	52 ^c
11	f	H	Me	i	y	89 ^c
12	g	H	F	i	z	42 ^c

^aReaction performed using 1 equiv of **4**, 1.05 equiv of **9**, 3 equiv of pyridine in CHCl_3 at 50 °C. ^bIsolated yield of **6** after silica gel chromatography; only product obtained. ^c3 equiv of **4** used.

(entries 4–6).^{11d} While the addition of dabco, phenanthroline, or pyridine did improve the yield, it plateaued at 78%. Using pyridine, a further improvement was realized by increasing the temperature of the reaction to 50 °C (entry 7). Next, we examined if the stoichiometry of our α -arylation could be reversed in order to enable the use of the 2-azidoaryllead acetate as a reagent for the α -arylation of more valuable β -ketoesters (entries 8 and 9). To our delight, we found that yield diminished only slightly, and if 3 equiv of **4a** was used, the yield recovered to 88%. Finally, we attempted the α -arylation in one-flask directly from 2-azidophenylboronic pinacolboronate ester **8a** without isolation the 2-azidoaryllead acetate to afford **6a** in 45% (entry 10).

Using these optimal conditions, a series of β -ketoesters were examined to determine the scope and limitations of our α -arylation reaction (Table 2). We found that the ring size of the β -ketoester could be modified without affecting the yield of our α -arylation reaction to provide functionalized aryl azides **6b–d** (entries 1–3). Acyclic β -ketoesters, such as **4e**, could even be smoothly converted to product without much attenuation of the yield (entry 4). Next, the effect of the composition of the β -ketoester on the yield of the arylation was examined (entries 5–7): indanone **9f**, 4-tetrahydropyranone **9g**, and 4-aminocyclohexanone **9h** produced aryl azides **6f–h** in good yields. To our surprise, while the α -arylation of amides has generated considerable excitement,^{16,17} γ -lactams have never been used in these processes despite the synthetic utility of these molecules. We found that they could be efficiently arylated to produce **6i**

Table 4. Conversion of Aryl Azides to 3H-Indoles



entry	#	aryl azide 6	3H-indole 7	%, yield ^a
1	a			96
2	b			>95 ^b
3	c			84
4	g			90
5	h			95
6	i			92
7	k			91

^aIsolated yield of 7 after silica gel chromatography. ^bAs determined using ¹H NMR spectroscopy; 3H-indole 7b rapidly decomposed upon exposure to air.

in good yield (entry 8). Next, the stereoselectivity of our α -arylation reaction was investigated. Exposure of 4-*tert*-butyl-substituted β -ketoester 9j to our reaction conditions furnished 6j with 10:1 diastereoselectivity (entry 9). To our delight, the selectivity was not affected by the size of the 4-substituent: the diastereoselectivity remained 10:1 when the 4-*tert*-butyl group was replaced with a smaller 4-phenyl group (entry 10). Finally, we examined the effect of changing the nature of the carboxylate group (entries 11–13). We found that an ester was necessary for the α -arylation reaction. While the methyl ester could be replaced with either an allyl or menthyl (albeit with no diastereoselectivity observed), β -ketoamides proved to be unreactive in our process.

The effect of adding substituents to the 2-azidoaryllead acetate on the α -arylation of β -ketoester 9a or γ -lactam 9i was examined next (Table 3). For β -ketoester 9a, we found that the arylation reaction tolerated halide, alkyl, or other substituents (entries 1–6). The yield, however, did depend on the electronic nature of 4 with the highest yields observed for the electron-rich or electron-neutral arylleads bearing methoxy- or methyl groups (entries 4 and 5). Further, the azide group could be placed at the 4-position without much diminishment of the yield of the arylation reaction (entry 7). To determine the generality of our reaction, we next examined the α -arylation of γ -lactam 9i, a substrate never reported as nucleophile in this process (entries 8–12).¹⁷ To our delight, we found that a range of different 2-azidoaryllead acetates reacted with γ -lactam 9i. Its

reactivity, however, was diminished in comparison to β -ketoester 9a. To obtain comparable yields, it was often necessary to increase the amount of the 2-azidoaryllead to 3 equiv (entries 10–12).

The synthetic utility of our α -arylation reaction was demonstrated next by exposing aryl azides 6 to a Staudinger reduction (Table 4).¹⁸ We found that exposure of aryl azides 6 to triphenylphosphine produced 3H-indoles 7 in nearly quantitative yield. Although the ring size of the β -ketoester could be modified in between the 5- and 7-carbons without affecting the Staudinger reaction, 3H-indole 7b readily decomposed when exposed to air (entries 1–3). The reduction tolerated heteroatoms in the β -ketoester to enable access to important *N*-heterocyclic structural motifs,¹⁹ such as γ -carboline 7h (entries 4 and 5). The Staudinger reaction could even be extended to γ -lactams to efficiently access 3H-pyrroloindole 7i in nearly quantitative yield (entry 6), whose structure is ubiquitous in bioactive alkaloids.²⁰ Finally, submission of aryl azide 6k to the reduction conditions furnished 3H-indole 7k in good yield without loss of any diastereoselectivity (entry 7). Together these results illustrate that when paired with a Staudinger reduction our α -arylation reaction to diastereoselectively access a range of 3H-indoles.

In conclusion, we developed an α -arylation reaction of β -ketoesters using 2-azidoaryllead acetates to afford a range complex, functionalized aryl azides with fully substituted *o*-alkyl substituents. The synthetic utility of our process was showcased using γ -lactam substrates to enable efficient construction of functionalized 3H-indoles after Staudinger reduction.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tgd@uic.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE-126563), National Institutes of Health NIGMS (R01GM084945), and the University of Illinois at Chicago for their generous support. We also thank Mr. Furong Sun for mass spectrometry data.

■ REFERENCES

- (1) For recent leading reviews, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Knölker, H.-J.; Reddy, K. R. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 2008; Vol. 65, pp 1–430. (d) Edwankar, C. R.; Edwankar, R. V.; Namjoshi, O. A.; Rallapappi, S. K.; Yang, S. J.; Cook, J. M. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 752. (e) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (f) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.
- (2) For recent, leading papers on their applications in electronic materials, see: (a) van Addy, D.; Bastiaansen, J. J. A. M.; Kiggen, N. M. M.; Langeveld, B. M. W.; Rothe, C.; Monkman, A.; Bach, I.; Stössel, P.; Brunner, K. J. *Am. Chem. Soc.* **2004**, *126*, 7718. (b) Wu, Y.; Li, Y.;

- Gardner, S.; Ong, B. S. *J. Am. Chem. Soc.* **2005**, *127*, 614.
- (c) Boudreault, P.-L. T.; Wakim, S.; Blouin, N.; Simard, M.; Tessier, C.; Tao, Y.; Leclerc, M. *J. Am. Chem. Soc.* **2007**, *129*, 9125. (d) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2011**, *112*, 2208.
- (3) For reviews, see: (a) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (b) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, *2011*, 4071.
- (4) cf. (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (c) Stokes, B. J.; Richert, K. J.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 6442. (d) Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 5920.
- (5) (a) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. *Org. Lett.* **2009**, *11*, 3598. (b) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262. (c) Nguyen, Q.; Nguyen, T.; Driver, T. G. *J. Am. Chem. Soc.* **2013**, *135*, 620.
- (6) For a discussion on the importance of step-economy in organic synthesis, see: (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
- (7) For reviews, see: (a) Hartwig, J. F. *Synlett* **2006**, 1283. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (c) Mazet, C. *Synlett* **2012**, 23, 1999.
- (8) For recent transition-metal-catalyzed examples, see: (a) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778. (b) Chernyak, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12466. (c) Donohoe, T. J.; Pilgrim, B. S.; Jones, G. R.; Bassuto, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11605. (d) Huang, Z.; Chen, Z.; Lim, L. H.; Quang, G. C. P.; Hirao, H.; Zhou, J. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5807. (e) Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7242.
- (9) For α -arylation using anilide derivatives, see: (a) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050. (b) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (c) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (d) Jiang, M.; Li, J.; Wang, F.; Zhao, Y.; Zhao, F.; Dong, X.; Zhao, W. *Org. Lett.* **2012**, *14*, 1420. (e) Wang, H.-Y.; Anderson, L. L. *Org. Lett.* **2013**, *15*, 3362. (f) Chan, W.-W.; Zhou, Z.; Yu, W.-Y. *Chem. Commun.* **2013**, *49*, 8214.
- (10) For leading reports on the α -arylation using I(III) reagents, see: (a) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673. (b) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516. (c) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149. (d) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (e) Review: Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *2011*, 517.
- (11) For leading examples of α -arylation using aryllead derivatives, see: (a) Review: Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, *57*, 5683. (b) Kozyrod, R. P.; Morgan, J.; Pinhey, J. T. *Aust. J. Chem.* **1985**, *38*, 1147. (c) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 715. (d) Dyer, J.; King, A.; Keeling, S.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2793. (e) Konopelski, J. P.; Lin, J.; Wenzel, P. J.; Deng, H.; Elliott, G. I.; Gerstenberger, B. S. *Org. Lett.* **2002**, *4*, 4121. (f) Buston, J. E. H.; Moloney, M. G.; Parry, A. V. L.; Wood, P. *Tetrahedron Lett.* **2002**, *43*, 3407. (g) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem.* **2007**, *72*, 6885.
- (12) For related noncatalyzed nucleophilic addition of enolates to other aromatic derivatives, see: (a) Ooi, T.; Goto, R.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 10494. (b) Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350. (c) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (d) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angélaud, R.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 1856. (e) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510. (f) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686. (g) Xu, Q.-L.; Gao, H.; Yousufuddin, M.; Ess, D. H.; Kürti, L. *J. Am. Chem. Soc.* **2013**, *135*, 14048.
- (13) For examples with more robust alkyl azides, see: (a) Ganina, O. G.; Zamotaeva, S. G.; Nosarev, M. A.; Kosenkova, O. V.; Naumov, M. I.; Shavryin, A. S.; Finet, J.-P.; Fedorov, A. Y. *Russ. Chem. Bull.* **2005**, *54*, 1606. (b) Naumov, M. I.; Nuchev, A. V.; Sitnikov, N. S.; Malysheva, Y. B.; Shavryin, A. S.; Beletskaya, I. P.; Gavryushin, A. E.; Combes, S.; Fedorov, A. Y. *Synthesis* **2009**, *2009*, 1673.
- (14) For the use of mercury or lead salts in the synthesis of biologically active small molecules for pharmaceutical applications, see: (a) Badham, N. F.; Chen, J.-H.; Cummings, P. G.; Dell'Orco, P. C.; Diederich, A. M.; Eldridge, A. M.; Mendelson, W. L.; Mills, R. J.; Novack, V. J.; Olsen, M. A.; Rustum, A. M.; Webb, K. S.; Yang, S. *Org. Process Res. Dev.* **2002**, *7*, 101. (b) Kuethe, J. T.; Childers, K. G.; Humphrey, G. R.; Journet, M.; Peng, Z. *Org. Process Res. Dev.* **2008**, *12*, 1201. (c) Wuts, P. G. M.; Ashford, S. W.; Conway, B.; Havens, J. L.; Taylor, B.; Hritzko, B.; Xiang, Y.; Zakarias, P. S. *Org. Process Res. Dev.* **2009**, *13*, 331.
- (15) The synthesis of 2-azidoarylboronic acid pinacolate esters **8** was not optimized. Although the 2-aminoarylboronic acid pinacolate esters precursors were synthesized for this study, all are commercially available. See the Supporting Information for more details.
- (16) Cf. (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274. (c) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344. (d) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900. (e) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190.
- (17) For leading reports of the use of the related oxindoles in α -arylation processes, see: (a) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613. (b) Mai, C.-K.; Sammons, M. F.; Sammakia, T. *Org. Lett.* **2010**, *12*, 2306. (c) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2870.
- (18) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. (b) Leffler, J. E.; Temple, R. D. *J. Am. Chem. Soc.* **1967**, *89*, 5235. (c) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (d) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
- (19) Cf. (a) Nguyen, C. H.; Lavelle, F.; Riou, J.-F.; Bissery, M.-C.; Huel, C.; Bisagni, E. *Anti-Cancer Drug Des.* **1992**, *7*, 235. (b) Gillonneau, L.; Pierré, A.; Charton, Y.; Guilbaud, N.; Kraus-Berthier, L.; Léonce, S.; Michel, A.; Bisagni, E.; Atassi, G. *J. Med. Chem.* **1999**, *42*, 2191. (c) Hopkins, C. R. *ACS Chem. Neurosci.* **2010**, *1*, 587.
- (20) cf. (a) Kobayashi, J.; Ishibashi, M. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Cordell, G. A., Eds.; Academic Press: San Diego, 1992; Vol. 41, pp 41–124. (b) Anthoni, U.; Christophersen, C.; Nielson, P. H. In *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1999; Vol. 13, pp 163–236.