Stereoselective Synthesis of 2-Dienyl-Substituted Pyrrolidines Using an η^4 -Dienetricarbonyliron Complex as the Stereodirecting Element: Elaboration to the Pyrrolizidine Skeleton

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Received May 9, 2006

2006 Vol. 8, No. 20 4389–4392



Primary amines react with keto-aldehyde functionality located in the side-chain of an η^4 -dienetricarbonyliron complex to provide the corresponding pyrrolidines in excellent diastereoselectivity. Two of the pyrrolidine products, 1i and 1k, have been elaborated into pyrrolizidines using a 1,5-C–H insertion and radical cyclization strategy, respectively.

de > 95%

Unsymmetrically substituted η^4 -dienetricarbonyliron complexes exhibit planar chirality and are readily prepared in enantiomerically pure form. As a consequence, this class of organometallic has become an important chiral auxiliary for stereoselective synthesis.¹ The steric blocking capability of the Fe(CO)₃ unit ensures that an external reagent approaches a side-chain functional group in a predictable fashion, attacking the diastereotopic face that is remote from the iron unit (Scheme 1). Providing the pendant functional group adopts a single reactive conformation, levels of diastereoselectivity can be excellent. The reaction of nucleophiles with pendant ketone functionality in η^4 -diene²—and related³— complexes provides a paradigm. In these cases, the stereochemical outcome of the reaction can be rationalized by assuming nucleophilic addition proceeds opposite the bulky $Fe(CO)_3$ group on the s-cis conformer of the ketone.^{2,3}

Our interest in 2-dienyl-substituted nitrogen heterocycles for potential application in natural product synthesis led us to propose a novel route to this framework using η^4 dienetricarbonyliron complexes (Scheme 1).⁴ Starting from keto-aldehyde complex **4**, a first reductive amination on the more electrophilic aldehyde would generate secondary amine **3**. Subsequent cyclization on to the proximal ketone, to afford a second iminium species **2**, followed by a second reductive amination, would then generate the corresponding pyrrolidine

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For reviews, see: (a) Knölker, H.-J. Curr. Org. Synth. 2004, 1, 309–331. (b) Ong, C. W.; Lai, M. C. Trends Organomet. Chem. 2002, 4, 47–58. (c) Donaldson, W. A. Curr. Org. Chem. 2000, 4, 837–868. (d) Knölker, H.-J. Chem. Rev. 2000, 100, 2941–2961. (e) Knölker, H.-J. Chem. Soc. Rev. 1999, 28, 151–157. (f) Cox, L. R.; Ley, S. V. Chem. Soc. Rev. 1998, 27, 301–314. (g) Iwata, C.; Takemoto, Y. Chem. Commun. 1996, 2497–2504. (h) Grée, R.; Lellouche, J.-P. Advances in Metal-Organic Chemistry 1995, 4, 129–273. (i) Grée, R. Synthesis 1989, 341–355. (j) Franck-Neumann, M. Pure Appl. Chem. 1983, 55, 1715–1732.

^{(2) (}a) González-Blanco, O.; Branchadell, V.; Grée, R. *Chem. Eur. J.* **1999**, 5, 1722–1727. (b) Franck-Neumann, M.; Chemla, P.; Martina, D. *Synlett* **1990**, 641–642. (c) Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, 92, 3058–3064.

^{(3) (}a) Ley, S. V.; Cox, L. R.; Meek, G.; Metten, K.-H.; Piqué, C.; Worrall, J. M. J. Chem. Soc., Perkin Trans. 1 **1997**, 3299–3313. (b) Ley, S. V.; Cox, L. R. J. Chem. Soc., Perkin Trans. 1 **1997**, 3315–3325.

⁽⁴⁾ For a novel application of this type of building block in the synthesis of elaeokanine C, see: Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153–1168.





1 in one step.⁵ The dienetricarbonyliron group would not only control the facial selectivity of the second reductive amination in this cascade sequence, but also ensure that reaction proceeds preferentially on a single conformer, which we predicted in this case would be the s-trans conformer, since this minimizes steric interactions between the diene ligand and appended functionality (Scheme 1).⁶ We now report the successful realization of this strategy.

The synthesis of the keto-aldehyde complex **4** is summarized in Scheme 2. Treatment of ethyl sorbate with [Fe₂-



(CO)₉] in Et₂O generated the corresponding diene complex, and acid **5** after saponification. Reaction of **5** with carbonyl diimidazole (CDI) and H₂NMe(OMe)Cl furnished the corresponding Weinreb amide **6** in excellent yield. Interestingly, carrying out this reaction under a CO_2 atmosphere led to a substantial increase in the rate of reaction.⁷ Reaction of the Grignard reagent prepared from commercially available 3-chloropropan-1-ol,⁸ with amide **6**, proceeded smoothly to afford keto-alcohol **7** in excellent yield, and thence keto-aldehyde cyclization precursor **4** after Swern oxidation.⁹

Although double reductive amination strategies have been successfully employed in pyrrolidine ring synthesis,⁵ yields of the desired product are often compromized by a competing Paal-Knorr reaction, which provides the corresponding pyrrole.^{5d,f,10} Thus when keto-aldehyde **4** was treated with BnNH₂ (1.2 equiv) in the presence of either NaCNBH₃¹¹ or NaBH(OAc)₃¹² and AcOH (1 equiv), it was unsurprising to find that the rather labile pyrrole product (60%) predominated, although the desired pyrrolidine **1a** was obtained in 21% yield. Fortunately, by removing the acid, pyrrole formation was efficiently suppressed, allowing the target pyrrolidine 1a to be isolated in good yield. More significantly, the stereoselectivity of the reaction was excellent with only one diastereoisomer being observed upon analysis of the crude reaction mixture by 300 MHz ¹H NMR. THF and 1,2-dichloroethane proved equally effective solvents for the reaction, and since similar yields of pyrrolidine were obtained with NaCNBH₃ and NaBH(OAc)₃, the lower toxicity issues associated with the latter, made NaBH(OAc)₃ the reagent of choice.

Extending this cascade double reductive amination to a range of primary amines showed this route to be a general approach to 2-dienyl-substituted pyrrolidines (Table 1). In

Tal	ble 1.	Diastereoselective Synthesis of Pyrrolidines 1 RNH ₂ , NaBH(OAc) ₃ 4 THF, rt, 12 h ^a H N 1 R		
	entrv	RNH ₂	Product	isolated %
		<u>4</u> -	1	yield ^b
	1	PhCH ₂ NH ₂	a	75 (8)
	2	<i>p</i> -MeOPhCH ₂ NH ₂	b	77 (5)
	3	(S) - α -methylbenzylamine	с	$71^{c} (4)^{d}$
	4	MeNH ₂	d	$60^{e}(6)$
	5	"BuNH ₂	e	67 (8)
	6	HOCH ₂ CH ₂ NH ₂	f	$70^{e,f}(7)$
	7	propargylamine	g	$50(7)^{d}$
	8	allylamine	h	$76(8)^d$
	9	Br MH ₂	i	$80^{g}(0)$
	10	TMS NH ₂	j	60 (0)
	11		k	78 (0)
	12		1	$70^{c} (2)^{d}$

^{*a*} The reaction is generally stirred overnight, although it is often complete in 4–6 h. ^{*b*} Numbers in parentheses refer to the isolated % yield of the corresponding pyrrole byproduct. ^{*c*} 1:1 mixture of diastereoisomers obtained. ^{*d*} The pyrrole product decomposed readily. ^{*e*} AcOH was used to reduce the reaction pH to ~6. ^{*f*} Isolated yield of the TBDMS-protected product (two steps). ^{*g*} *E/Z* ratio ~ 5:1. all cases only one configuration at the newly formed stereocenter was observed. Significantly, pyrrolidines 1c and 11, which were formed from enantiomerically pure amines, (S)- α -methylbenzylamine and (S)-phenylalaninol, respectively, were obtained as a 1:1 mixture of diastereoisomers, which clearly shows that the planar chirality of the diene complex overrides the chirality of the amine. The standard reaction conditions proved suitable for all substrates apart from particularly basic amines such as methylamine and ethanolamine, where the high reaction pH (>10) led to exclusive pyrrole formation. In these cases, reducing the reaction pH to 6 solved this problem and allowed the desired pyrrolidine (1d, 1f) to be obtained in good yield.¹⁰ It proved impossible to access the free pyrrolidine directly: the use of NH₃ led to a complex mixture of products, and when NH₄-HCO₂ was employed, only the pyrrole was obtained.^{5e} However the free pyrrolidine 8 was readily accessed by deallylation of **1h** (Scheme 3).¹³



Confirmation of the stereochemical outcome of the cyclization reactions came from crystal structures (see the Supporting Information) of the pyrrolidine (*Z*)-**1i** and amide **9**, formed from **1h** after deallylation and acylation (Scheme 3). In both cases, the observed diastereoselectivity was the

(5) For some recent successful applications of this approach to pyrrolidines, see: (a) Laventine, D. M.; Davies, M.; Evinson, E. L.; Jenkins, P. R.; Cullis, P. M.; Fawcett, J. *Tetrahedron Lett.* **2005**, *46*, 307–310. (b) Gravier-Pelletier, C.; Maton, W.; Bertho, G.; Le Merrer, Y. *Tetrahedron* **2003**, *59*, 8721–8730. (c) Trost, B. M.; Schroeder, G. M.; Kristensen, J. Angew. Chem., Int. Ed. **2002**, *41*, 3492–3495. (d) Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. J. Chem. Soc., Perkin Trans. 1 **2002**, 143– 154. (e) Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Yokoyama, M. J. Org. Chem. **1998**, *63*, 7207–7212. (f) Boga, C.; Manescalchi, F.; Savoia, D. Tetrahedron **1994**, *50*, 4709–4722.

(6) For related reactions that also proceed on iminium ions appended to diene complexes, see: (a) Takemoto, Y.; Takeuchi, J.; Matsui, E.; Iwata, C. *Chem. Pharm. Bull.* **1996**, *44*, 948–955. (b) Ripoche, I.; Gelas, J.; Grée, D.; Grée, R.; Troin, Y. *Tetrahedron Lett.* **1995**, *36*, 6675–6678.

(7) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P. J. Org. Chem. **2004**, 69, 2565–2568.

(8) Turakhia, R. H.; Fischer, G. C.; Morrow, C. J.; Maschhoff, B. L.;
Toubbeh, M. I.; Zbur-Wilson, J. L. J. Org. Chem. 1986, 51, 1955–1960.
(9) Grée, D. M.; Martelli, J. T.; Grée, R. L.; Toupet, L. J. J. Org. Chem.

1995, 60, 2316–2317.

(10) (a) Raiman, M. V.; Pukin, A. V.; Tyvorskii, V. I.; De Kimpe, N.; Kulinkovich, O. G. *Tetrahedron* **2003**, *59*, 5265–5272. (b) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. J. Am. Chem. Soc. **2003**, *125*, 2058–2059.

(11) Borch, R. F.; Bernstein, M. D.; Durst, H. D. J. Am. Chem. Soc. 1971, 93, 2897–2904.

(12) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. Tetrahedron Lett. **1990**, 31, 5595–5598.

(13) Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J. M. Tetrahedron Lett. 1995, 36, 1267–1270.

same, and in line with our hypothesis that the second reductive amination proceeds on the iminium intermediate in an s-trans conformation, with "hydride" attack from the face remote from the bulky tricarbonyliron group.

Having established an efficient and highly stereoselective route to 2-dienyl-substituted pyrrolidines, we were keen to explore the possibility of employing the vinyl bromide functionality present in **1i** and **1k** as an entry into the biologically important pyrrolizidine skeleton.¹⁴

In the case of **1k**, Cu(II)-mediated decomplexation afforded pyrrolidine **10** in 70% yield.¹⁵ While we expected a vinyl radical formed from bromide **10** would cyclize preferentially on to the pendant diene in a 5-exo-trig fashion, the stereoselectivity of this cyclization and regioselectivity in the subsequent H-abstraction step, could still afford a host of isomeric products. It was therefore pleasing to observe that reaction of **10** with Bu₃SnH in the presence of AIBN, provided pyrrolizidine **13** as a >10:1 mixture of vinylsilane stereoisomers. The fact that the stereochemistry of the vinylsilane in the major product is opposite to that in the starting material is in accord with the known configurational instability of vinyl radicals.¹⁶ The diastereoselectivity of the reaction is consistent with cyclization proceeding on vinyl radical **11** through the transition state shown in Scheme 4.



The position of the alkene in the side-chain can then be rationalized by assuming H-abstraction proceeds on the less hindered end of the resulting allyl radical intermediate **12**.

In an alternative elaboration strategy, we envisaged that treating vinyl bromide **1i** with base should afford a carbenoid

⁽¹⁴⁾ Liddell, J. R. Nat. Prod. Rep. 2002, 19, 773-781 and references therein.

⁽¹⁵⁾ Thompson, D. J. J. Organomet. Chem. 1976, 108, 381-383.

⁽¹⁶⁾ Vinyl radicals are known to be configurationally unstable. For a pertinent example, see: Miura, K.; Itoh, D.; Hondo, T.; Hosomi, A. *Tetrahedron Lett.* **1994**, *35*, 9605–9608.

intermediate, which would generate another pyrrolizidine through a stereospecific 1,5-C–H insertion reaction.^{17,18} Since literature precedent suggested that this might occur regioselectively at the more substituted carbon,^{18b,19} this transformation would then provide a useful route into challenging systems containing a defined quaternary stereogenic center.

After some optimization,²⁰ it was found that treatment of **1i** with KHMDS in 1,4-dioxane at room temperature provided a 3:1 mixture of insertion products **14** and **15** in 55% combined yield (Scheme 5). The Fe(CO)₃ group in both



14 and 15 was readily removed by treatment with basic peroxide²¹ to afford the free dienes, 17 and 18, respectively, in excellent yield (Scheme 5). Interestingly, when the 1,5-C-H insertion was performed on the free diene 16 under our optimized conditions, the yield of insertion products, 17 and 18, improved to 86%. However, this was at the expense of regioselectivity, which dropped to 1:1 (Scheme 5). We

tentatively suggest that the improved regioselectivity observed in the 1,5-insertion reaction involving diene complex **1i** is a consequence of the $Fe(CO)_3$ group generating a sterically more crowded methine center than is present in free diene **16**. This should result in lengthening, and concomitant weakening, of the methine C–H bond in the diene complex favoring insertion into this bond. Anchimeric assistance from the iron complex also electronically activating the methine center in **1i** may also be a factor in the improved regioselectivity associated with the iron complex.^{1e}

In summary, an η^4 -dienetricarbonyliron complex containing a keto-aldehyde side-chain has been used in a cascade, double reductive amination reaction to provide the corresponding 2-substituted pyrrolidine in excellent diastereoselectivity. The $Fe(CO)_3$ moiety plays a crucial role in the reaction, controlling the facial selectivity of "hydride" attack in the second reductive amination and ensuring reaction proceeds on a single iminium ion conformation. Since diene complexes bearing carboxylic acid functionality, such as 5, which is a key intermediate in our synthesis, are readily prepared in enantiopure form, either by enzymatic resolution,^{22d} or through the use of chiral auxiliaries,^{22a-c} this approach can also be used to access the corresponding enantiomerically pure series of N-heterocycles. The pyrrolidine products are ripe for elaboration into pyrrolizidines, which have been accessed in a variety of ways. Of particular note here, the Fe(CO)₃ moiety affects the regioselectivity of a 1,5-C-H insertion with reaction favoring the pyrrolizidine containing a stereodefined quaternary stereogenic center. Future work will focus on using the diene that is released upon decomplexation in the synthesis of more complex polycyclic frameworks.

Acknowledgment. We are grateful to Pfizer for an industrial CASE studentship to I.W.

Supporting Information Available: General experimental procedures and characterization data for all new compounds and X-ray crystallographic files (CIF) for compounds (*Z*)-**1i** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061132L

⁽¹⁷⁾ Gabaitsekgosi, R.; Hayes, C. J. Tetrahedron Lett. **1999**, 40, 7713–7716.

^{(18) (}a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. J. Org. Chem. **1985**, 50, 2557–2563. (b) Karpf, M.; Huguet, J.; Dreiding, A. S. Helv. Chim. Acta **1982**, 65, 13–25.

⁽¹⁹⁾ Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. J. Org. Chem. **1983**, 48, 5251–5256.

⁽²⁰⁾ LDA, LiHMDS, NaHMDS, and KHMDS were investigated in Et₂O, THF, and 1,4-dioxane at rt. The method of carbene/carbenoid generation, including the choice of base and solvent, has been shown to influence the regioselectivity: (a) Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927–4930 and references therein. (b) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. J. Org. Chem. **1999**, *64*, 9673–9678.

⁽²¹⁾ Franck-Neumann, M.; Heitz, M. P.; Martina, D. Tetrahedron Lett. **1983**, *24*, 1615–1616.

⁽²²⁾ See for example: (a) Pearson, A. J.; Chang, K.; McConville, D. B.; Youngs, W. J. *Organometallics* **1994**, *13*, 4–5. (b) Franck-Neumann, M.; Briswalter, C.; Chemla, P.; Martina, D. *Synlett* **1990**, 637–640. (c) de Montarby, L.; Tourbah, H.; Grée, R. *Bull. Soc. Chim. Fr.* **1989**, 419–432. (d) Alcock, N. W.; Crout, D. H. G.; Henderson, C. M.; Thomas, S. E. *J. Chem. Soc., Chem. Commun.* **1988**, 746–747.