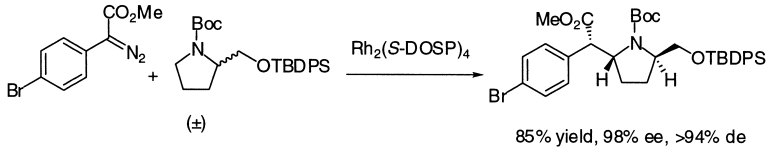
Article

New Strategic Reactions for Organic Synthesis: Catalytic Asymmetric C–H Activation to Nitrogen as a Surrogate for the Mannich Reaction

Huw M. L. Davies, Chandrasekar Venkataramani, Tore Hansen, and Darrin W. Hopper

J. Am. Chem. Soc., **2003**, 125 (21), 6462-6468• DOI: 10.1021/ja0290072 • Publication Date (Web): 01 May 2003



More About This Article

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

- Supporting Information
- Links to the 11 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
ARTICLES
Published on Web 05/01/2003

New Strategic Reactions for Organic Synthesis: Catalytic Asymmetric C−H Activation α to Nitrogen as a Surrogate for the Mannich Reaction

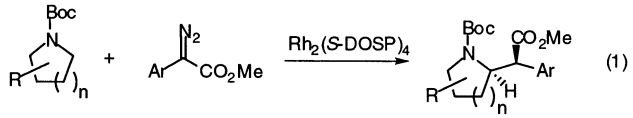
Huw M. L. Davies,* Chandrasekar Venkataramani, Tore Hansen, and Darrin W. Hopper

Contribution from the Department of Chemistry, University at Buffalo, State University of New York, Buffalo, New York 14260-3000

Received October 18, 2002; E-mail: hdavies@acsu.buffalo.edu

Abstract: The asymmetric C−H activation reactions of methyl aryldiazoacetates are readily induced by the rhodium prolinate catalyst Rh_2(*S*-DOSP)$_4$ (**1**) or the bridged prolinate catalysts Rh_2(*S*-biDOSP)$_2$ (**2a**) and Rh_2(*S*-biTISP)$_2$ (**2b**). The C−H activation of *N*-Boc-protected cyclic amines demonstrates that the donor/acceptor-substituted carbenoids display remarkable chemoselectivity, which allows for highly regioselective, diastereoselective, and enantioselective reactions to be achieved. Furthermore, the reactions can display high levels of double stereodifferentiation and kinetic resolution. The C−H activation is caused by a rhodium carbenoid induced C−H insertion. The potential of this chemistry is demonstrated by a very direct synthesis of *threo*-methylphenidate.

The development of practical methods that would achieve functionalization of unactivated C−H bonds is of considerable current interest.[1,2] Recently, we reported a very general method for intermolecular C−H activation by means of a rhodium carbenoid induced C−H insertion.[3,4] High asymmetric induction can be achieved in this C−H activation process when these reactions are catalyzed by dirhodium tetraprolinates. The reaction is applicable to a wide range of substrates, and because of subtle steric and electronic effects it is highly chemoselective. We have previously communicated that asymmetric C−H activation can occur α to *N*-Boc-protected cyclic amines (eq 1).[3c,d] This paper will give a full description of the scope of this chemistry, with particular emphasis on the effect of ring size and the factors that control the chemoselectivity and diastereoselectivity. A further focus will be on the robust double diastereoselection and kinetic resolution that is achievable with this system. A particularly attractive feature of this methodology is that the products are β-amino acid derivatives, and so it may be considered as a new strategic reaction that is a surrogate for the Mannich reaction.[5]



(1)

The successful development of the asymmetric intermolecular C−H activation by rhodium carbenoids required much more chemoselective carbenoid intermediates than the carbenoids derived from diazoacetates, which had been typically used.[6,7]

(1) For reviews on other methods for C−H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *28*, 1698. (c) Arndsten, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (f) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

(2) For recent representative examples of C−H activation, see: (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Waltz, K. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 11358. (c) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (d) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (e) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (f) Saaby, S.; Bayon, P.; Aburel, P. S.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352. (g) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202. (h) Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 1378.

(3) (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383. (d) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509. (e) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (f) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153. (g) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2071. (h) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773. (i) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587.

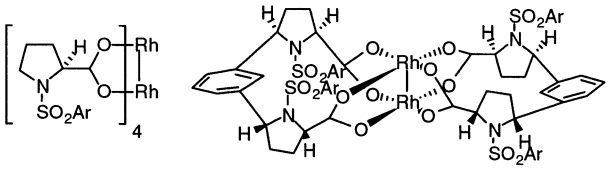
(4) For recent reviews, see: (a) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 45. (b) Davies, H. M. L. *J. Mol. Catal. A* **2002**, *189*, 125.

(5) For reviews and recent references on the catalytic asymmetric Mannich reaction, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (d) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (f) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (g) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (h) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (i) Cordova, A.; Watanabe, S.-i.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (j) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (k) List, B. *Synlett* **2001**, 1675.

(6) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 112−162. (b) Mass, G. *Topics in Current Chemistry*; Springer-Verlag: New York, 1987; Vol. 137, pp 75−254.

10.1021/ja0290072 CCC: $25.00

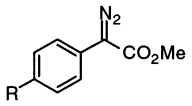
Donor/acceptor-substituted carbenoids, where the donor group is aryl or vinyl, display this enhanced chemoselectivity.[8] When these carbenoids are generated by the rhodium prolinate catalyst Rh_2(*S*-DOSP)$_4$ (**1**)[9] or the bridged prolinate catalysts Rh_2(*S*-biDOSP)$_2$ (**2a**) and Rh_2(*S*-biTISP)$_2$ (**2b**),[10] highly enantioselective transformations are commonly observed. In this study of the scope of the C−H activation, the aryldiazoacetates **3a** and **3b** were used as the carbenoid source. Rh_2(*S*-DOSP)$_4$ was used as the primary catalyst, while Rh_2(*S*-biDOSP)$_2$ (**2a**) and Rh_2(*S*-biTISP)$_2$ (**2b**) were used as back-up on the rare occasions when poor enantioselectivity was obtained with Rh_2(*S*-DOSP)$_4$.



1: Ar = $C_{12}H_{25}C_6H_4$ (Rh_2(*S*-DOSP)$_4$)

2a: Ar = *p*-$C_{12}H_{25}C_6H_4$ (Rh_2(*S*-biDOSP)$_2$)

2b: Ar = 2,4,6-^{i}PrC$_6$H$_2$ (Rh_2(*S*-biTISP)$_2$)

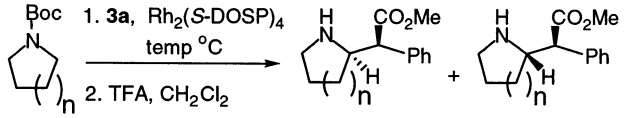


3a: R = H

3b: R = Br

The evaluation of various *N*-Boc amines as substrates for the C−H activation was carried out using a standard protocol. Because of the fact that the catalysts are air-, moisture-, and heat-stable,[11] the reactions can be conducted in a very straightforward and reproducible manner. Typically, the catalyst and substrate are placed in a hydrocarbon solvent under argon, and the aryldiazoacetate, dissolved in a hydrocarbon solvent, is added dropwise, and then the reaction mixture is stirred for an extended time. Most reactions can be conveniently conducted at room temperature, but depending on the reactivity of the substrates, reaction temperatures from −50 to 50 °C may be used. With substrates that are very active toward C−H activation, hexane is a suitable solvent, but with less active substrates, 2,2-dimethylbutane is a superior inert solvent.[3e] As is typical of most carbenoid reactions, an excess of the trapping agent may be used. However, because of the enhanced chemoselectivity of the donor/acceptor-substituted carbenoids, it is also possible to conduct these reactions effectively with the trapping agent as the limiting reagent.[3g] The products can be analyzed as their *N*-Boc derivatives, but often it is more convenient to remove the Boc protecting group with trifluoroacetic acid before analyzing the product.

Table 1. Effect of Ring Size on C−H Activation into *N*-Boc-Protected Cyclic Amines



4 **5** **6**

compound	*n*	temp, °C	yield, % (**5** + **6**)	ratio (**5**:**6**)	ee of **5**, %	ee of **6**, %
a	1	25	75	95:5	88	*a*
a	1	−50	72	96:4	94	*a*
b	2	25	86	50:50	79	25
b	2	−50	44	64:36	89	68
c	3	25	72	>95:5	92	*a*
d	4	25	74	>95:5	90	*a*

[a] Not determined.

Test reactions with cyclic amines of different ring sizes quickly revealed that subtle factors were involved in the efficiency of this chemistry. The five-, seven-, and eight-membered cyclic *N*-Boc amines were found to be excellent substrates, resulting in very efficient C−H insertion (Table 1). The reactions could be conveniently carried out at room temperature using 1 mol % of catalyst. Under these conditions, the diastereoselectivity and the enantioselectivity were exceptional. With *N*-Boc-pyrrolidine (**4a**), the *erythro* C−H insertion product **5a** was formed in 94% ee and 92% de, and similar high stereoselectivity was obtained with the seven- and eight-membered substrates **4c** and **4d**. In contrast, *N*-Boc-azetidine formed a complex mixture of products, while *N*-Boc-piperidine (**4b**) gave the C−H insertion products **5b** and **6b**, but the stereoselectivity was very different from the reactions of **4a**, **4c**, and **4d**. At room temperature, the *erythro* and *threo* products **5b** and **6b** were formed as a 1:1 diastereomeric mixture in 79% ee and 25% ee. The enantioselectivity could be improved by conducting the reaction at −50 °C, and under these conditions the *erythro* and *threo* products **5b** and **6b** were formed in 89% ee and 68% ee, respectively, with the *threo* isomer **6b** slightly predominating.

The surprising difference in stereochemistry between the various ring sizes prompted us to determine if the ring size has an impact on the reactivity toward C−H activation. Competition studies between pairs of systems revealed that *N*-Boc-piperidine is 20 times less reactive that the other cyclic amines (eq 2). As the *N*-Boc-piperidine is aligned in a well-defined chair conformation, it is conceivable that an axial position C−H bond is electronically favored for C−H activation but is sterically not favored. The five-, seven-, and eight-membered rings will be more conformationally flexible and may better accommodate the transition state for the C−H activation. In intramolecular reactions with the highly reactive carbenoids derived from diazoacetate derivatives, the C−H insertion preferentially occurs at equatorial C−H bonds.[12] Similar extreme differences in reactivity have been observed between the asymmetric lithiation reactions of *N*-Boc-piperidine and *N*-Boc-pyrrolidine, which are

(7) (a) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322. (b) Ambramovitch, R. A.; Roy, J. *J. Chem. Soc., Chem. Commun.* **1965**, 542. (c) Adams, J.; Poupart, M.-A.; Greainer, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749. (d) Callott, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321. (e) Callott, H. J.; Metz, F. *Nouv. J. Chim.* **1985**, *9*, 167. (f) Domenceau, A.; Noels, A. F.; Costa, J. L.; Hubert, A. *J. Mol. Catal.* **1990**, *58*, 21.
(8) Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. S. *Tetrahedron Lett.* **1998**, *39*, 4417.
(9) Davies, H. M. L.; Bruzinski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
(10) Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287.
(11) (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, *2459*, 9. (b) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107.
(12) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; Basten, A.; Mueller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.

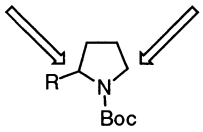
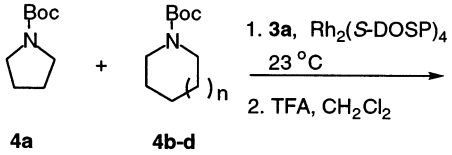
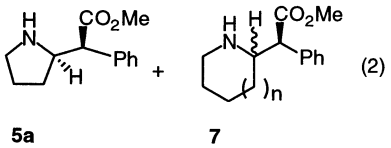


Figure 1. Competing sites for C−H activation in 2-substituted pyrrolidines.

caused by subtle stereoelectronic effects.[13]





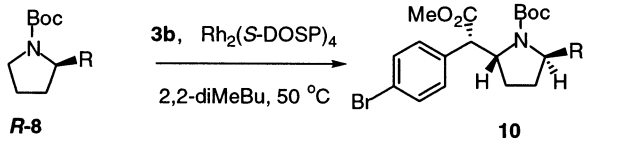
(2)

n	5a : 7
1	95 : 5
2	52 : 48
3	57 : 43

Having discovered that *N*-Boc-pyrrolidine is an exceptional substrate for the C−H activation, we then performed further experiments on 2-substituted pyrrolidines (Figure 1). These substrates were used to explore the selectivity issues of this chemistry. Not only would there be two distinct C−H insertion sites α to nitrogen, but also additional functionality could be present on the 2-substituent. A further intriguing component would be the effect of the stereogenic center at the 2 position. Matched and mismatched reactions would be possible as well as chiral catalyst induced kinetic resolution.[14]

To evaluate the effect of double stereodifferentiation on the C−H activation, the reaction of the two enantiomers of the *tert*-butyldiphenylsilyl (TBDPS) alcohol **8a** was examined. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of the aryldiazoacetate **3b** (2 equiv) at 50 °C in the presence of (*R*)-**8a** gave a remarkable reaction (eq 3). The C−H activation product **9** was obtained in 85% yield as a single diastereomer. The relative stereochemistry of **9** was readily confirmed on the basis of nOe analysis and the distinctive chemical shifts for the C-4 protons.[15] The reaction demonstrates the remarkable chemoselectivity that is possible in the C−H activation step because **8a** contains multiple C−H bonds including three sites that are adjacent to oxygen or nitrogen. Because of steric factors, however, only the methylene group adjacent to nitrogen is accessible to the rhodium carbenoid complex. A further attractive feature of the donor/acceptor carbenoids is the enhanced stability of the carbenoid, as this allows the elaborate trapping agent to be used as the limiting agent. In sharp contrast to the reaction with (*R*)-**8a**, the reaction of (*S*)-**8a** under identical conditions failed to give any C−H insertion product (eq 4). With this substrate, the only obvious product was carbene dimer.[3e]

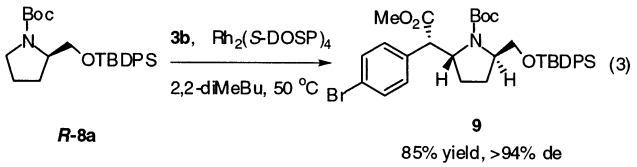
Table 2. Matched C−H Activation of 2-Substituted Pyrrolidines



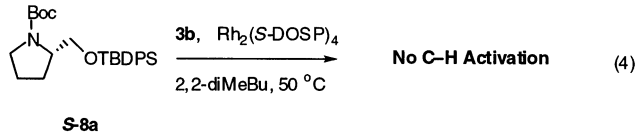
***R*-8** **10**

compound	R	yield, %	de, %
b	CO_2Me	83	>94
c	$CO_2{}^tBu$	85	>94
d	CH_2OAc	92	>94
e	CH_2OTBS	62[a]	>94

[a] After deprotection of the Boc group.



(3)



(4)

Matched C−H activations of a series of 2-substituted pyrrolidines **8b**−**e** were examined, and in all cases a highly efficient and diastereoselective reaction was observed to form **10** (Table 2). The stereochemistry of these reactions was assigned on the basis of nOe analysis and the distinctive chemical shifts for the C-4 protons.[15] Further confirmation was obtained by conversion of all of the products **10b**−**e** to a common alcohol.

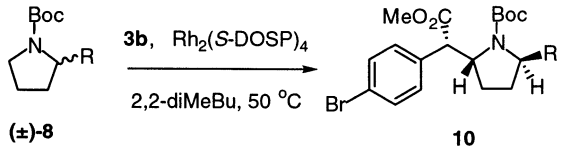
Unlike the very bulky TBDPS-derivative **8a**, the mismatched reactions of **8b**, **8d**, and **8e** gave rise to C−H activation products, but the results were variable. All three substrates gave rise to a diastereomeric mixture of C−H activation products in low yield, which indicates that the strong directing effects of both the substrate and the catalyst are competing against each other and are closely balanced. This is nicely demonstrated in the comparison of the results for (*S*)-**8b**, which gives rise to the two diastereomers **11** and **12** (eq 5). The formation of **11** is an especially interesting product because the asymmetric induction at the carbenoid site is opposite to that typically obtained with Rh_2(*S*-DOSP)$_4$, indicating that the substrate is the dominating stereocontrol element. The reaction with (*S*)-**8d**−**e** gives preferentially the cis product **13** (eq 6), which indicates that with this substrate the catalyst dominates the stereochemical outcome. The stereochemistry of all of these products was readily confirmed on the basis of nOe analysis and the distinctive

(13) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (b) Gross, K. M. B.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(14) Enantiomer differentiation and double stereodifferentiation by use of chiral catalysts have been reported for intramolecular cyclopropanation and C−H insertion. (a) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (b) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. (c) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.

(15) The relative stereochemistry is readily determined on the basis of distinctive chemical shifts in the proton NMR. For details, see: Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.

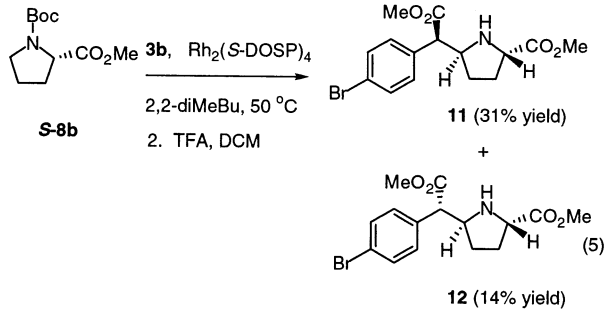
Table 3. Kinetic Resolution in C−H Activation of 2-Substituted Pyrrolidines



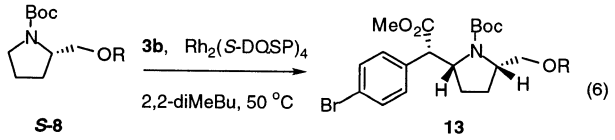
(±)-8 10

compound	R	equiv of (±)-**8**	yield, %	ee, %	de, %
b	CO_2Me	2	64	77	86
b	CO_2Me	4	66	79	86
c	$CO_2{}^tBu$	2	58	83	>94
c	$CO_2{}^tBu$	4	60	87	>94
d	CH_2OAc	2	58	88	76
d	CH_2OAc	4	62	94	78

chemical shifts for the C-4 protons.[15]



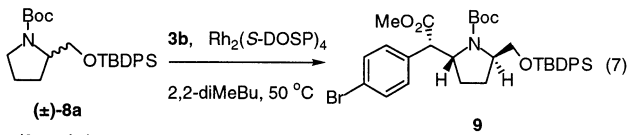
S-8b



S-8 13

d: R = Ac, 20% yield
e: R = TBS, 25% yield

The next series of experiments explored the possibility of obtaining kinetic resolution in this chemistry. Because of the fact that two new stereogenic centers were formed in this reaction, the focus of this work was on the efficient formation of the enantioenriched product rather than the enrichment of the starting material. As expected from the results described in eqs 3 and 4, the reaction with (±)-**8a** gave a spectacular result. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of the aryldiazoacetate **3b** at 50 °C in the presence of (±)-**8a** (2 equiv) gave the C−H insertion product **9** as a single diastereomer in 98% ee (eq 7). This result again convincingly demonstrates that the mismatched C−H activation with (*S*)-**8a** is a very unfavorable process.



(±)-8a (2 equiv.) 9

85% yield, 98% ee, >94% de

Kinetic resolution was also explored with (±)-**8b**−**d**, and the results are summarized in Table 3. In these cases, the diastereoselectivity and enantioselectivity are lower than those with (±)-**8a** because the mismatched reactions are competing reactions and give different diastereomeric mixtures of products as compared to the matched reactions. As expected, there is a slight improvement in diastereoselectivity and enantioselectivity on using 4 equiv instead of 2 equiv of the trapping agent. The enantioselectivity observed in these products is due to a combination of the kinetic resolution and the enantiomer differentiation induced by the chiral catalyst.

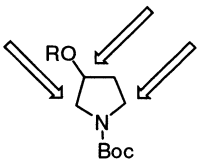
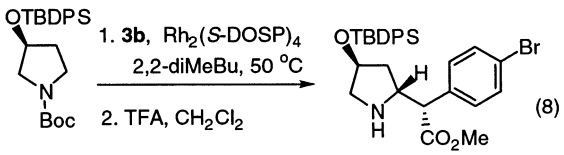


Figure 2. Competing sites for C−H activation in 3-substituted pyrrolidines.

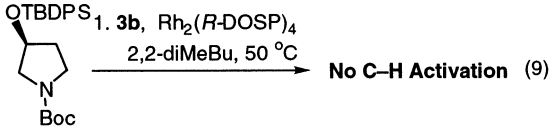
The studies were then extended to 3-substituted pyrrolidines (Figure 2). These substrates add further challenge to the chemistry because these compounds contain two methylene sites adjacent to the nitrogen, and so very subtle effects would be required to achieve effective regiocontrol.

The matched and mismatched reactions with the TBDPS-protected alcohol **14a** gave very impressive double stereodifferentiation. The matched reaction of (*S*)-**14a** with **3b** (2 equiv) catalyzed by Rh_2(*S*-DOSP)$_4$ at 50 °C gave the C−H activation product **15** as a single diastereomer in 69% yield (eq 8). The stereochemical assignment of **15** was initially determined on the basis of nOe analysis and the distinctive chemical shifts.[15] In contrast, the mismatched reaction of (*S*)-**14a** with Rh_2(*R*-DOSP)$_4$ as catalyst failed to give any C−H activation product (eq 9). The only obvious product was carbene dimer.[3e]



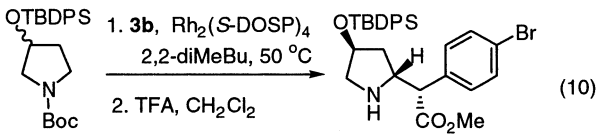
S-14a 15

69% yield, >94% de



S-14a

The high double stereodifferentiation observed with **14a** is indicative that (±)-**14a** would be an excellent candidate for kinetic resolution. Indeed the reaction of (±)-**14a** (2 equiv) with **3b** catalyzed by Rh_2(*S*-DOSP)$_4$ at 50 °C gave the C−H insertion product **15** as a single diastereomer in >99% ee (eq 10).

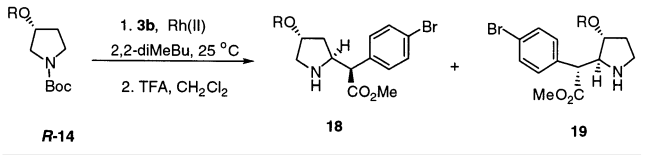


(±)-14a (2 equiv.) 15

64% yield, >94% de, >99% ee

The effect of a smaller substituent at the C-3 position resulted in a further refinement of this chemistry. The matched reaction

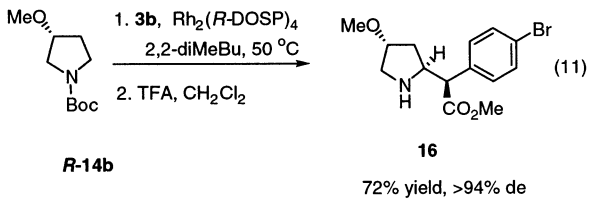
Table 4. Enantiomer Differentiation in C−H Activation of 3-Substituted Pyrrolidines

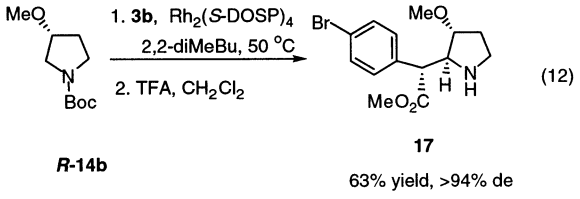


compound	R	Rh(II)	**18**, yield, %	**18**, de %	**19**, yield, %	**19**, de %
c	TBS	Rh_2(*R*-DOSP)$_4$	71	>94	*a*	
d	TMS	Rh_2(*R*-DOSP)$_4$	73	>94	*a*	
d	TMS	Rh_2(*S*-DOSP)$_4$	*b*		50	>94
e	Ac	Rh_2(*R*-DOSP)$_4$	70	>94	*a*	
e	Ac	Rh_2(*S*-DOSP)$_4$	94	50	41	>94

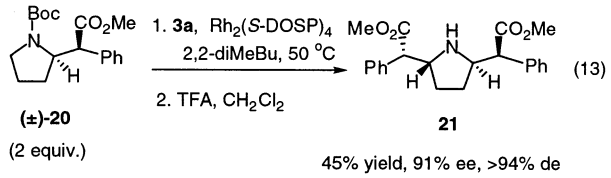
[a] None observed in the proton NMR of the crude reaction mixture. [b] Trace observed (<5%) in the proton NMR of the crude reaction mixture.

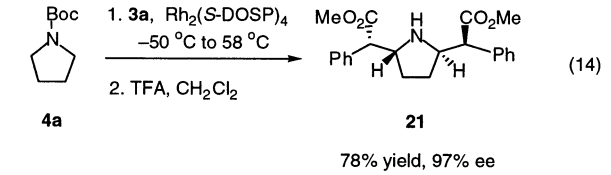
of the methyl ether (*R*)-**14b** with Rh_2(*R*-DOSP)$_4$ catalyst proceeded uneventfully and generated the C−H activation product **16** as a single diastereomer in 72% yield (eq 11). In contrast, the mismatched reaction gave a mixture of C−H insertion products in which the major product **17** formed in 63% yield was derived from C−H activation at the C-2 position (eq 12). This C-2 insertion product, which is tentatively assigned as **17**, was also formed with very high diastereoselectivity. These results represent a very novel example of enantiomer differentiation by the chiral catalyst leading to different regioisomeric products. Similar results were obtained with **14c**−**e**, and these are summarized in Table 4.





Having demonstrated that kinetic resolution is possible in the substituted pyrrolidines, we were intrigued to determine if the initial product of the C−H activation was capable of undergoing a second C−H activation. The racemic C−H insertion product (±)-**20** was most conveniently prepared by reaction of **3a** with **4a** using a 1:1 mixture of the (*R*)- and (*S*)-DOSP catalysts. The traditional achiral catalysts such as rhodium acetate and rhodium octanoate are not especially effective in this chemistry, presumably because the carbenoid is not sufficiently electrophilic.[3f] Reaction of (±)-**20** with **3a** in the presence of Rh_2(*S*-DOSP)$_4$ catalyst resulted in the formation of **21** in 91% ee (eq 13). A further development would be if C−H activation at both sites could be carried out in a single reaction flask. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **3a** (6.0 equiv) in the presence of *N*-Boc-pyrrolidine (**4a**) gave **21** in 78% yield and 97% ee (eq 14). The higher enantioselectivity that is obtained as compared to that obtained in the initial C−H activation step reveals that double diastereoselection is occurring in the second C−H activation step.





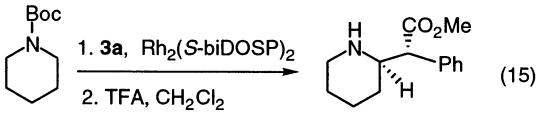
The reaction between the methyl phenyldiazoacetate (**3a**) and *N*-Boc-piperidine (**4b**) is a very significant reaction because it represents a very direct entry for the asymmetric synthesis of *threo*-methylphenidate **6b** (Ritalin).[16] As the Rh_2(*S*-DOSP)$_4$-catalyzed reactions with *N*-BOC-piperidine were not highly stereoselective (Table 1), optimization studies were carried out using the bridged prolinate catalysts. A major improvement in enantioselectivity and diastereoselectivity was achieved by carrying out the reaction with the bridged prolinate catalysts (eq 15). In the reaction catalyzed by Rh_2(*S*-biDOSP)$_2$, the ratio of **6b**:**5b** was 2.7:1 (73% combined yield), and (2*R*,2′*R*)-*threo*-isomer **6b** was isolated in 86% ee and 52% yield. Comparable results were also obtained using Rh_2(*S*-biTISP)$_2$ as catalyst. It is well established that the bridged prolinate catalysts result in opposite asymmetric induction to Rh_2(*S*-DOSP)$_4$,[4,10] and in the reaction of **3a** and **4b** catalyzed by either Rh_2(*S*-biDOSP)$_2$ or Rh_2(*S*-biTISP)$_2$, the biologically active enantiomer of *threo*-methylphenidate (**6b**) is formed. Winkler has also examined the reaction between **3a** and *N*-Boc-piperidine and reported[17] that Rh_2(*S*-MEPY)$_4$ gave the best results, a 45% yield of **5b** and **6b** in a 94:6 ratio, with **6b** formed in 69% ee. In our efforts to reproduce these results with Rh_2(*R*-MEPY)$_4$, we obtained **6b** in 53% ee, but the diastereoselectivity (64% de) and the combined yield of **5b** and **6b** (22%) were considerably lower than reported.[18] A brief study was conducted with piperidines having other nitrogen protecting groups. Different carbamates such as methoxycarbonyl can be used, but this does not have much of an impact on the stereoselectivity of the C−H activation. In contrast, the use of an amide protecting group such as *N*-acetyl totally blocks the C−H activation chemistry. Instead, a very unproductive reaction occurs with evidence of

(16) For other approaches to the asymmetric synthesis of *threo*-methylphenidate, see: (a) Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem.* **1998**, *41*, 591. (b) Prashad, M.; Kim, H.; Lu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750. (c) Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Org. Lett.* **1999**, *1*, 175.

(17) Axten, J. M.; Ivy, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6511.

(18) The discrepancy between our results with Rh_2(*R*-MEPY)$_4$ as compared to those of Winkler's study (ref 17) is uncertain. Winkler, however, reported the de for **6b** after chromatographic purification of the initial Boc-protected product and trituration of the HCl salt of **6b**, which could have led to diastereomeric enrichment.

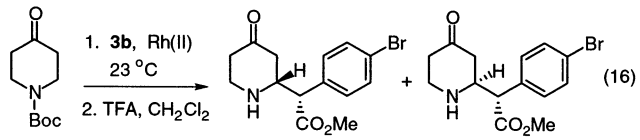
some products derived from ylide intermediates.



4b **ent-6b**

52% yield, 86% ee

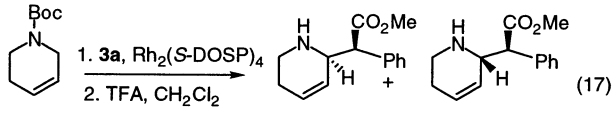
Even though the *N*-Boc-piperidine system is 20 times less reactive toward C−H activation than that of *N*-Boc-pyrrolidines, studies were carried out to determine if C−H activation would still occur with substituted piperidines. Neither 3-siloxy- nor 4-siloxypiperidines underwent efficient C−H activations, even under forcing conditions. Consequently, piperidine systems containing sp^2 hybridized centers were examined because they would be unable to adopt a well-defined chair conformation. The reaction of *N*-Boc-piperidin-4-one (**22**) was a favorable reaction, resulting in the formation of a 2:1 mixture of the C−H activation products **23** and **24** (eq 16). Once again, the enantioselectivity was highest with Rh_2(*S*-biTISP)$_2$ (**2b**), but the diastereoselectivity was not influenced by the catalyst in this case.



22 **23** **24**

Rh_2(*S*-DOSP)$_4$	31% yield (83% ee)	20% yield (53% ee)
Rh_2(*S*-biTISP)$_2$	46% yield (88% ee)	23% yield (76% ee)

Another efficient substrate was *N*-Boc-1,2,3,6-tetrahydropyridine (**25**). In this case, the major diastereomer was the *erythro* product **26**. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **3a** in the presence of **25** (4 equiv) in 2,3-dimethylbutane at room temperature followed by treatment with TFA resulted in a 63% yield of C−H insertion products **26** and **27** (eq 17). Remarkably, the *erythro* diastereomer **26** was the major diastereomer (62% de) and was isolated in 53% yield and 80% ee. Determination of the relative and absolute stereochemistry of **26** as (2*S*,2′*R*) was readily achieved by conversion of **26** to *erythro*-methylphenidate **5b** by catalytic hydrogenation.



25 **26** **27**

26 : **27** = 4.6 : 1

26, 80% ee; **27**, 55% ee

A similar preference for five-membered rings as substrates for the C−H activation was also seen in benzo fused systems. Neither *N*-Boc-protected tetrahydroquinoline nor tetrahydroisoquinoline were effective substrates for this chemistry, yet a very clean reaction was obtained with the *N*-Boc-protected indoline **28** (eq 18). Rh_2(*R*-DOSP)$_4$-catalyzed decomposition of **3b** in the presence of **28** in refluxing 2,2-dimethylbutane, followed by deprotection of the Boc group with TFA, resulted in the formation of the C−H activation product **29** in 38% yield as a single diastereomer in 90% ee. The relative stereochemistry was assigned on the basis of distinctive shielding by the phenyl ring.[15]

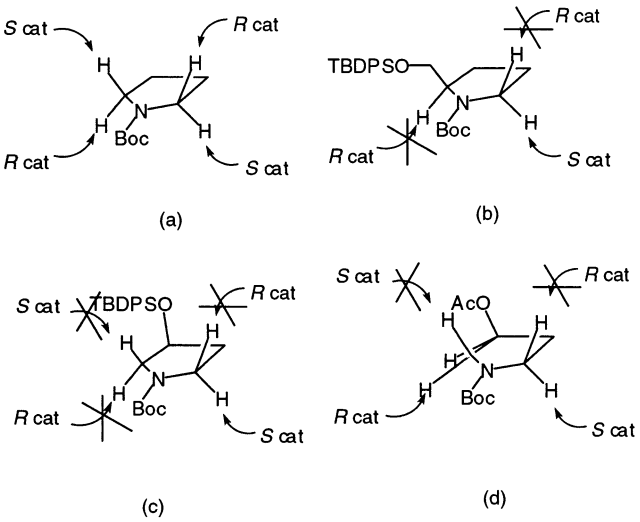
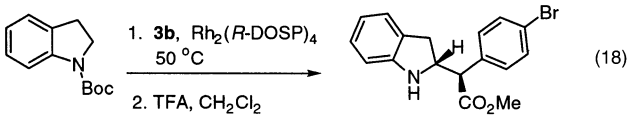


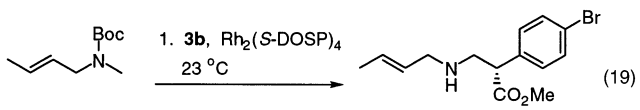
Figure 3. Selectivity of C−H activation of substituted pyrrolidines.



28 **29**

38% yield, >94% de, 90% ee

The C−H activation reactions of *N*-Boc-protected cyclic amines emphatically demonstrate the remarkable chemoselectivity that is possible with this chemistry. It has already been demonstrated that C−H activation preferentially occurs at sites that can stabilize buildup of positive charge at the carbon.[4] Thus, benzylic and allylic sites as well as sites adjacent to oxygen and nitrogen are favored. This is counterbalanced by steric effects as the rhodium carbenoid behaves as a very sterically encumbered species. The steric effects are readily seen in the C−H activation of the 2-substituted pyrrolidines because the tertiary site adjacent to nitrogen is not reactive even though it is electronically the most activated site. Another dramatic example of the steric effects has been described in a recent article on the C−H activation chemistry of acyclic amines (eq 19).[19] In this case, no C−H activation occurs at the electronically favored allylic site, but instead C−H activation of the *N*-methyl group occurs.



30 **31**

58% yield, 85% ee

(19) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197.

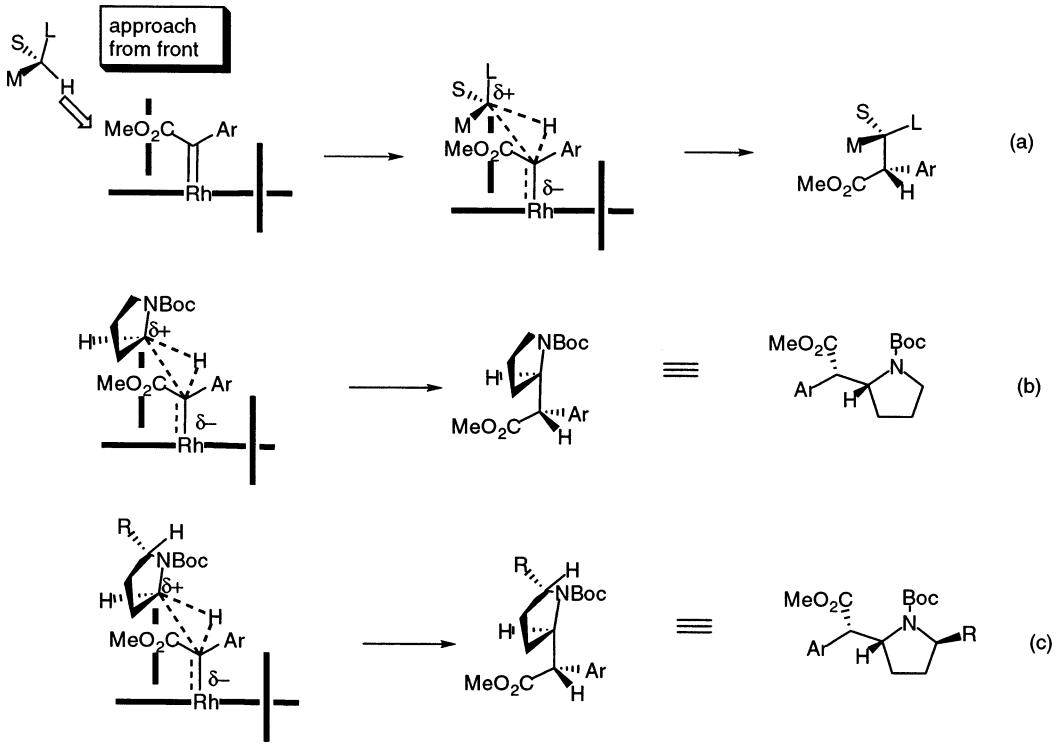


Figure 4. Predictive model for C−H activation stereoselectivity with (a) a generic alkane, (b) *N*-Boc pyrrolidine, and (c) 2-substituted *N*-Boc pyrrolidine.

The general rules with regard to enantioselectivity and regioselectivity of the C−H activation chemistry are summarized in Figure 3. In the unsubstituted case (Figure 3a), Rh_2(*S*-DOSP)$_4$-catalyzed reactions have a strong preference for C−H insertion into the *pro*-H_R hydrogen. In the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of the 2-substituted pyrrolidines, only a (2*R*)-substituent will avoid interference with the *pro*-*R* C−H bond at C-5. Thus, (2*R*)-substituted prolines result in a matched reaction (Figure 3b), while the (2*S*)-substituted prolines result in mismatched reactions. By a similar argument, the reaction of Rh_2(*S*-DOSP)$_4$ catalyst with the (3*S*)-substituted prolines results in a matched reaction (Figure 3c), while the reactions of Rh_2(*R*-DOSP)$_4$ catalyst with the (3*S*)-substituted prolines result in matched reactions.[20] If the (3*S*)-substituent is large, no C−H activation is observed, while if it is relatively small, enantiomer differentiation is observed, and C−H activation occurs at the C-2 carbon instead of the C-5 carbon observed in the matched reaction (Figure 3d).

The absolute stereochemistry of this reaction is in agreement with the predictive model we have developed for this chemistry. Rh_2(*S*-DOSP)$_4$ is considered to behave as a D_2 symmetric complex and can be simply considered as having two blocking groups on either rhodium face.[11] Although the exact trajectory of the carbenoid in this system is not known, it is proposed that the C−H activation is a concerted nonsynchronous process and that the substrate approaches over the carbenoid electron-withdrawing group, with the arrangement of the large (L), medium (M), and small (S) groups as drawn (Figure 4a).[4] Placement of pyrrolidine in this arrangement would predict that the (2*R*,2′*R*) product would be formed (Figure 4b). Similarly, (2*S*)-substituted prolines would be the matched reaction because the (2*S*)-substituent would be pointing away from the rhodium carbenoid complex (Figure 4c). The unexpected result is the diastereoselectivity of the *N*-Boc-piperidine system, but it is anticipated that subtle stereoelectronic effects are operating in the reaction with this system.

In summary, the C−H activation of cyclic amines demonstrates that the donor/acceptor-substituted carbenoids display remarkable chemoselectivity, which allows for highly regioselective, diastereoselective, and enantioselective reactions to be achieved. Furthermore, the reactions can display high levels of double stereodifferentiation and kinetic resolution. A most attractive feature of this chemistry is that elaborate chiral cyclic amines are readily formed, and many of these products could be useful scaffolds to compounds of pharmaceutical interest.

Acknowledgment. Financial support of this work by the National Science Foundation (CHE 0092490) and the National Institutes of Health (DA06301 and DA15225) is gratefully acknowledged. Some confirmatory studies by Mr. Abbas Walji are gratefully acknowledged.

Supporting Information Available: Experimental section and details regarding stereochemical assignments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0290072

(20) For consistency with the other figures in Figure 3, the representation in Figure 3d shows the predicted outcome for an Rh_2(*S*-DOSP)$_4$-catalyzed reaction with the (3*S*)-substituted prolines. The actual reactions that were conducted in this paper were the Rh_2(*R*-DOSP)$_4$-catalyzed reaction with the (3*R*)-substituted prolines.