ORGANIC LETTERS

2004
Vol. 6, No. 11
1769−1772

Double C–H Activation Strategy for the Asymmetric Synthesis of C_2-Symmetric Anilines

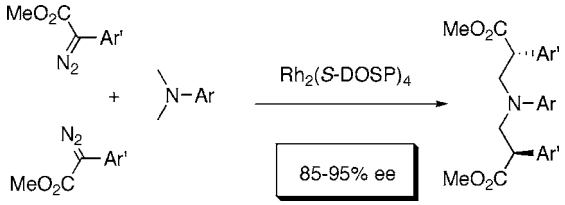
Huw M. L. Davies* and Qihui Jin

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

hdavies@acsu.buffalo.edu

Received March 10, 2004

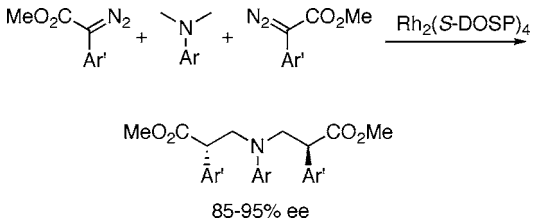
ABSTRACT



Rh_2(*S*-DOSP)$_4$-catalyzed C–H activation to *N*,*N*-dimethylanilines is described. A double C–H activation was possible by using an excess of methyl aryldiazoacetate, and this provided a very direct approach to C_2-symmetric anilines.

In recent years, there has been considerable interest in developing practical methods for achieving C−H activation.[1,2] Such methods would offer exciting new strategies for the construction of complex synthetic targets. We have recently shown in a series of papers that intermolecular C−H insertion by rhodium-carbenoids represents a general method for asymmetric C−H activation.[3] This approach can be considered as a surrogate to some of the classic reactions of organic synthesis such as the aldol reaction,[4] the Mannich reaction,[5] the Michael reaction,[6] and the Claisen rearrangement.[7] In this paper, we describe the application of this chemistry to the asymmetric synthesis of C_2-symmetric anilines (Scheme 1).

Scheme 1



Intermolecular C−H insertion by rhodium carbenoids derived from ethyl diazoacetate was demonstrated to be a feasible reaction 30 years ago.[8] On the basis of these early

(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.

(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) 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.

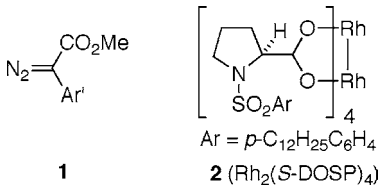
(4) (a) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153.

(5) (a) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509. (b) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773. (c) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197.

(6) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2071.

10.1021/ol0495467 CCC: $27.50
Published on Web 04/29/2004

studies, however, the reaction was not considered to be of significant synthetic utility because the carbenoids displayed poor chemoselectivity.[9] The breakthrough in this chemistry came about with the development of donor/acceptor-substituted carbenoids because these carbenoids are much more chemoselective than the traditional carbenoids lacking the donor group.[10] Classic examples of donor/acceptor-substituted carbenoids are those derived from aryldiazoacetates **1**, which undergo highly enantioselective reactions when Rh_2(*S*-DOSP)$_4$ (**2**) is used as catalyst (Figure 1).[3] A delicate balance of electronic and steric effects controls the remarkable chemoselectivity displayed by these carbenoids. C−H insertion is preferred at sites that stabilize positive charge buildup on the carbon.[3] The rhodium-carbenoid, however, is sterically very demanding, and steric issues often dominate over the electronic preference.



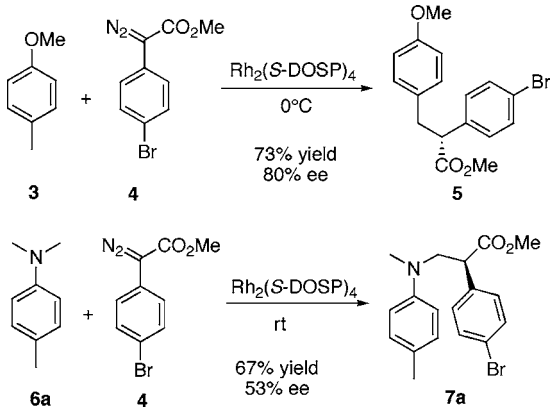
1 **2** (Rh_2(*S*-DOSP)$_4$)

Figure 1. Carbenoid precursor and catalyst.

The initial discovery that led to this current paper arose during studies on benzylic C−H activation.[11,12] A Hammett study had shown that electron-donating substituents in the aromatic ring strongly enhance the C−H activation chemistry at the benzylic position.[12] A very impressive example is the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of *p*-methylanisole (**3**) with methyl *p*-bromophenyldiazoacetate (**4**), which results in the formation of **5** in 73% yield and 80% ee (Scheme 2).[11] On the basis of this result, it was anticipated that *N*,*N*-dimethyl-*p*-toluidine (**6a**) would be an even better substrate for benzylic C−H activation. Indeed, **6a** undergoes a very clean C−H activation with **4**, but unexpectedly, the product that is formed is the regioisomer **7a** (67% yield, 53% ee), arising from C−H insertion into the *N*-methyl group.[13] Intrigued by the efficiency of the formation of **7a**, we have undertaken a systematic study on the C−H activation chemistry of *N*,*N*-dimethylanilines.

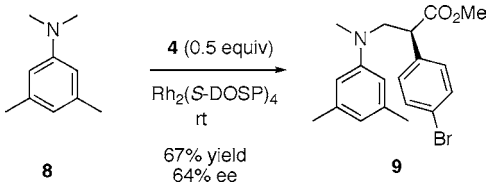
We have previously demonstrated that electron-rich aromatic rings are not susceptible to electrophilic substitution

Scheme 2



reactions with donor/acceptor-substituted carbenoids if the aromatic ring is sterically encumbered (at least 1,4-disubstituted).[11,12] 3,5-Dimethyl-*N*,*N*-dimethylaniline (**8**) would be expected to be a good substrate for C−H activation because it should be too sterically crowded for electrophilic aromatic substitution. As predicted, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **8** with **4** was very efficient, resulting in the formation of the C−H insertion product **9** in 67% yield and 64% ee (Scheme 3).

Scheme 3



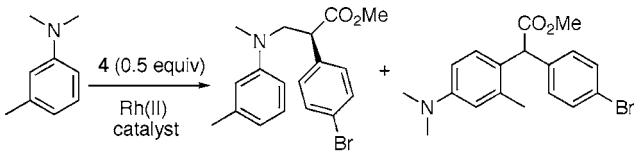
To explore more thoroughly the effect of steric hindrance of the aromatic ring toward electrophilic substitution, the reaction of *N*,*N*-dimethyl-*m*-toluidine (**10**) was examined. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **10** with **4** gave a 2:3 mixture of the C−H insertion product **11** and the electrophilic substitution product **12** in a combined yield of 60% (Scheme 4). **11** was produced in 64% ee, while **12** was essentially racemic. The ratio of the products is very dependent on the catalyst used because the same reaction catalyzed by rhodium octanoate gave a 4:1 mixture of **11** and **12** (30% combined yield).

N,*N*-Dimethylaniline (**13**) is not sterically protected from electrophilic substitution, and not surprisingly, this is the dominant reaction between **13** and **4** (Scheme 5). Even so, some of the C−H activation product **14** is also formed and the ratio of **14** and the electrophilic substitution product **15** is very dependent on the catalyst and solvent. Electron-deficient catalysts enhance electrophilic substitution over

(7) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587.
(8) (a) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, *14*, 2233. (b) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (c) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc. Chim. Belg.* **1984**, *93*, 945. (d) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Mol. Catal.* **1988**, *49*, L13.
(9) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 112−162.
(10) Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. S. *Tetrahedron Lett.* **1998**, *39*, 4417.
(11) Davies, H. M. L.; Jin, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 941.
(12) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.

(13) Stereochemical assignment for **7**, **9**, **11**, **14**, **18**, and **20** is derived from the predictive model for C−H activation catalyzed by Rh_2(*S*-DOSP)$_4$. See ref 3 for details.

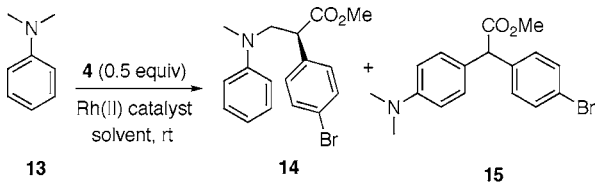
Scheme 4



catalyst	11 : 12	11+12, yield, %	11, ee, %
Rh_2(*S*-DOSP)$_4$	2 : 3	60	64
Rh_2(OOct)$_4$	4 : 1	30	

C−H activation, and so does the use of dichloromethane instead of a hydrocarbon solvent. The optimum conditions for the formation of the electrophilic substitution product **15** are Rh_2(*S*-DOSP)$_4$ as the catalyst and dichloromethane as the solvent.

Scheme 5



catalyst	solvent	14 : 15	14, yield, %	15, yield, %
Rh_2(*S*-DOSP)$_4$	$CH_3CH_2C(CH_3)_3$	7 : 93	4	64
Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	1 : 99	--	78
Rh_2(TFA)$_4$	$CH_3CH_2C(CH_3)_3$	3 : 97	--	45
Rh_2(OOct)$_4$	$CH_3CH_2C(CH_3)_3$	35 : 65	9	15

Over the years we have described several examples of how the product outcome is dependent on subtle solvent and catalyst effects.[14] Hydrocarbon solvents and electron-rich catalysts favor reactions occurring through relatively uncharged intermediates/transition states, while polar solvents and electron-deficient catalysts favor reactions occurring via zwitterionic intermediates. The catalyst and solvent effects observed here are consistent with this interpretation because the C−H activation is considered to involve a concerted nonsynchronous transition state,[3] as represented by **16**, and the aromatic substitution occurs via the zwitterionic intermediate **17** (Figure 2).[15] Presumably, the rhodium in **17** is released prior to the proton transfer, as this would explain why the electrophilic substitution products are formed without asymmetric induction.

The reaction can be extended to a range of *p*-substituted *N*,*N*-dimethylanilines **6**, and the results are summarized in Table 1. The reaction is fairly uniform over a range of

(14) (a) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299. (b) Davies, H. M. L.; Clark, T. J.; Kimmer, G. F. *J. Org. Chem.* **1991**, *56*, 6440. (c) Davies, H. M. L.; Clark, T. J. *Tetrahedron* **1994**, *50*, 9883.

(15) Davies, H. M. L.; Smith, H. D.; Hu, B.; Klenzak, S. M.; Hegner, F. J. *J. Org. Chem.* **1992**, *57*, 6900.

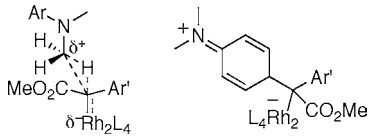
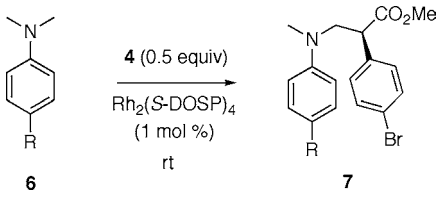


Figure 2. Proposed intermediates/transition states.

substrates, giving the C−H activation products **7** in 51−72% yield and 53−71% ee. A most notable example is the reaction with the *p*-(silyloxymethylene) derivative **6f** because C−H activation cleanly occurs at the *N*-methyl sites in favor of the electonically very activated benzylic position.

Table 1. C−H Activation of *N*,*N*-Dimethylanilines



	R	yield, %	ee, %
a	Me	67	53
b	*t*-Bu	60	58
c	F	70	58
d	Br	72	56
e	CO_2Me	51	71
f	CH_2OTBS	70	61

The high reactivity of the aniline *N*-methyl group toward C−H activation was a promising indication that *N*,*N*-dimethylanilines might be susceptible to double C−H activation. We had previously reported that *N*-Boc-pyrrolidines were capable of double C−H activation, but 6 equiv of diazo compound and elevated temperatures were required to achieve such a transformation.[5a] The double C−H activation of 3,5-dimethyl *N*,*N*-dimethylaniline (**8**) was readily achieved by simply altering the stoichiometry of the reaction by using 2.2 equiv of the diazo compound and 2 mol % of the catalyst. Under these conditions, a 2.4:1 mixture of the C_2-symmetric product **18** and the meso diastereomer **19** was formed, from which **18** was obtained in 57% yield (Scheme 6). Gratifyingly, the C_2-symmetric product **18** was formed in 95% ee,

Scheme 6

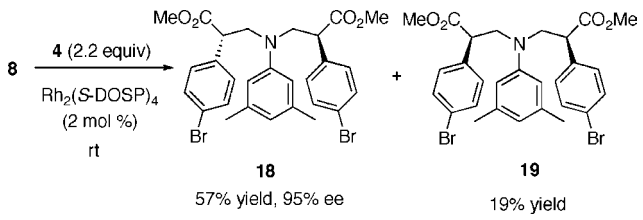
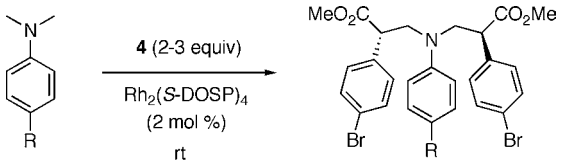


Table 2. Double C−H Activation of *N*,*N*-Dimethylanilines



20

substrate	R	product	yield, %	ee, %
6a[a]	Me	**20a**	41	91
6b[b]	*t*-Bu	**20b**	55	91
6c[b]	F	**20c**	60	89
6d[b]	Br	**20d**	60	90
6e[b,c]	CO_2Me	**20e**	54	85
6f[d]	CH_2OTBS	**20f**	42	92

[a] Performed with 2 equiv of **4**. [b] Performed with 3 equiv of **4**. [c] Reaction was conducted at 50 °C. [d] Performed with 2.5 equiv of **4**.

which indicates that the second C−H activation occurred with the same sense of asymmetric induction as the first C−H activation. Consequently, the C_2-symmetric product **18** is produced with much higher ee than the initial C−H activation product **9**.

The reaction can be extended to the synthesis of a series of C_2-symmetric anilines **20** as summarized in Table 2. The asymmetric induction is uniformly high (85−92% ee). C_2-symmetric amines have wide utility as chiral ligands in asymmetric synthesis,[16] and the very rapid access to a novel class of C_2-symmetric amines underscores the synthetic potential of the C−H activation chemistry.

It has been generally assumed that the success of the intermolecular C−H activation chemistry is due to the unique reactivity profile of donor/acceptor-substituted carbenoids.[10] To test this hypothesis, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of two of the traditional diazo compounds, ethyl diazoacetate and dimethyl diazomalonate, with *N*,*N*-dimethyl-*p*-toluidine (**6a**) was examined. It was anticipated that a very different product outcome would result, but in fact neither ethyl diazoacetate nor dimethyl diazomalaonate was effectively decomposed by Rh_2(*S*-DOSP)$_4$ in the presence of **6a**.

In summary, this paper further demonstrates the remarkable chemoselectivity of the C−H activation chemistry of donor/acceptor-substituted carbenoids. *N*,*N*-Dimethylanilines are very favorable substrates when the aromatic ring is sterically protected toward electrophilic substitution. The double C−H activation of *N*,*N*-dimethylanilines represents a very direct approach for the synthesis of structurally elaborate C_2-symmetric anilines. Further studies are in progress to determine the utility of derivatives of these C_2-symmetric anilines as ligands for asymmetric synthesis.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0350536).

Supporting Information Available: Experiment procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0495467

(16) (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (c) Takahata, H.; Kouno, S.; Momose, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1085.