JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Double-Asymmetric Hydrogenation Strategy for the Reduction of 1,1-Diaryl Olefins Applied to an Improved Synthesis of CuIPhEt, a C_2-Symmetric N-Heterocyclic Carbenoid

Elizabeth Spahn,[†] Abigail Albright,[†] Michael Shevlin,[‡,*] Larissa Pauli,[§] Andreas Pfaltz,[§,*] and Robert E. Gawley[†,*]

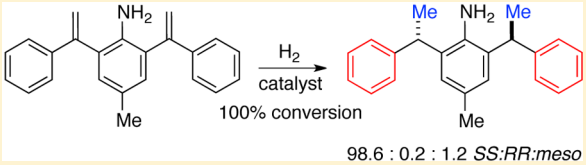
[†]Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701, United States

[‡]Department of Process Chemistry, Merck and Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065, United States

[§]Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Supporting Information

ABSTRACT: A library of iridium and rhodium phosphine catalysts have been screened for the double-asymmetric hydrogenation of 2,6-di-(1-phenylethenyl)-4-methylaniline to produce the C_2-symmetric aniline precursor of the N-heterocyclic carbenoid CuIPhEt. The best catalyst produced the desired enantiomer in 98.6% selectivity. This rare example of a highly selective hydrogenation of a 1,1-diaryl olefin enables a four-step asymmetric synthesis of the C_2-symmetric phenylethyl imidazolium ion (IPhEt) from *p*-toluidine and phenylacetylene and its conversion to the hydrosilylation catalyst CuIPhEt.



N-Heterocyclic carbenes have risen to prominence in recent years as ligands in transition-metal catalysis and as organic catalysts.[1−8] The versatility of the *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr) ligand[9] led us to explore the synthesis and structure of several imidazolium heterocycles having a stereocenter γ to the imidazolium nitrogen.[10] The Cu(I) complex of one of these ligands, which we call CuIPhEt (I for imidazolium, PhEt for phenethyl, Figure 1), was shown to be extraordinarily selective in the hydrosilylation of aryl alkyl and dialkyl ketones.[11] To our knowledge, there is no other asymmetric hydrosilylation or hydrogenation catalyst that matches CuIPhEt in its enantioselectivity in the reduction of dialkyl ketones. A typical CuIPhEt hydrosilylation is performed at room temperature in THF for less than 60 min with 2 mol % catalyst loading.[11] Ten examples were reported with good yields and excellent enantioselectivities. In the presence of CuIPhEt, the hydrosilylation of acetophenone, the benchmark test for catalysts in this category, gives a 99:1 er in 90% yield after 45 min at room temperature. Especially noteworthy is the hydrosilylation of 2-butanone and 3-heptanone, which proceeded in 98:2 and 95:5 er, respectively.

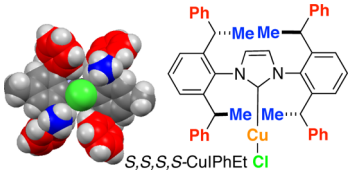
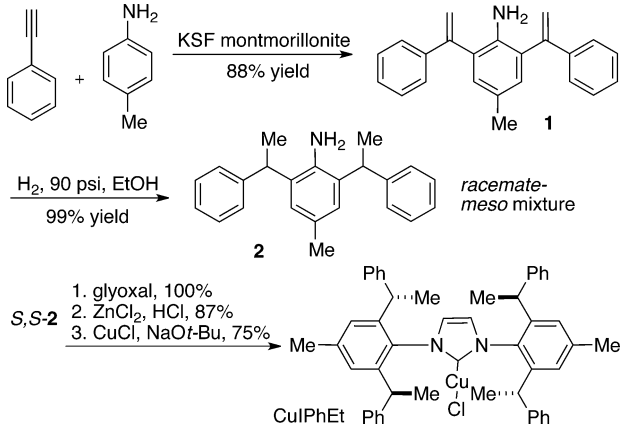


Figure 1. X-ray crystal structure of CuIPhEt.[10]

In our first synthesis of CuIPhEt (Scheme 1),[10] we used Sartori's procedure[12] to prepare aniline **1** by condensation of phenylacetylene with *p*-toluidine. Hydrogenation then afforded a mixture of racemic and *meso* anilines **2**, which were separated by chiral stationary phase chromatography. The chiral enantiomers were then separately condensed with glyoxal, cyclized, deprotonated, and added to CuCl to give CuIPhEt in 65% yield over the three steps. X-ray crystallography revealed a beautiful chiral pocket surrounding the copper atom (Figure 1). Because of the excellent selectivity exhibited by CuIPhEt in

Scheme 1



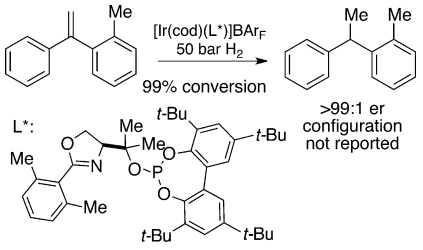
Received: December 5, 2012
Published: February 5, 2013

   dx.doi.org/10.1021/jo3026548 | J. Org. Chem. 2013, 78, 2731−2735

hydrosilylations and because of the potential for new applications of the IPhEt ligand in both organocatalysis and transition-metal catalysis, we investigated the possibility of an asymmetric hydrogenation of **1** to *S,S*-**2** and *R,R*-**2**. This approach seemed attractive because of the statistical benefit of two consecutive asymmetric reactions. Assuming that both C=C bonds were reduced under catalyst control, with little influence of the stereogenic center formed in the first hydrogenation step, high enantioselectivity could be expected even if the facial selectivies of the individual steps were only moderate.

Disubstituted terminal alkenes are a challenging substrate class for asymmetric hydrogenation compared to the more widely studied trisubstituted olefins.[13−16] Although Marks and co-workers reported the asymmetric hydrogenation of 2-phenyl-1-butene in 98:2 er at −80 °C in 1992, the chiral organosamarium complex they used did not find further application due to the difficult preparation and high sensitivity of this catalyst system.[17,18] Iridium complexes based on chiral P,N ligands provided a more practical solution in this case, as they are less sensitive to air and moisture and are easy to handle. It was found that the enantioselectivity in the hydrogenation of 2-phenyl-1-butene strongly depended on the hydrogen pressure with best results achieved at 1 atm of H_2. Under these conditions, a range of 2-aryl-1-butenes was hydrogenated with high enantioselectivites of up to 97:3 er.[19,20] Until recently, no examples of asymmetric hydrogenation of diaryl-substituted terminal alkenes were known. However, in a combined effort, the groups of Börner, Andersson, and Diéguez showed that excellent enantioselectivities can be obtained with substrates of this type using sterically very demanding phosphite−oxazoline ligands (Scheme 2).[21] In view of these results, we decided to screen a library of iridium complexes in the hydrogenation of diene **1** and the corresponding *N*-acetyl derivative.

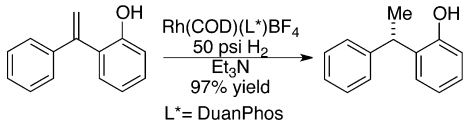
Scheme 2



While iridium P,N ligand complexes are the catalysts of choice for the asymmetric hydrogenation of olefins lacking any coordinating substituents, rhodium− and ruthenium−diphosphine complexes perform best with functionalized olefins bearing a coordinating group next to the C=C bond: 2-acetamidoacrylic acid derivatives are typical examples.[22] A recent example of phenol-directed rhodium-catalyzed asymmetric hydrogenation of 1,1-diarylethenes was reported by Wang and co-workers (Scheme 3).[23] By analogy, because the amino group of diene **1** or the acetamido group of the *N*-acetylated substrate are both potential coordinating groups, we included a series of rhodium−diphosphine catalysts in our study.

Herein, we report the results of a survey of a library of enantioselective hydrogenation catalysts, the most selective of

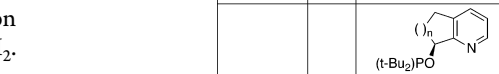
Scheme 3



which results in outstanding stereoselectivity for the formation of one of the chiral stereoisomers.

The search for an effective catalyst for the asymmetric hydrogenation of aniline **1** entailed screening of libraries of both iridium- and rhodium-based catalysts (Table 1).

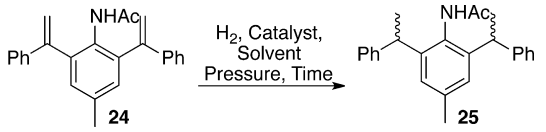
Table 1. Catalyst Library (See the Supporting Information for Structures)

Catalyst	M^+	Ligand	X^-
3	Rh	(*S,S*)-DIOP	Cl^-
4	Rh	(*R,R*)-Chiraphos	Cl^-
5	Rh	(*R,R*)-Skewphos	Cl^-
6	Rh	(*R,R*)-Norphos	Cl^-
7	Rh	(*M*)-BINAP	Cl^-
8	Ir	(4*S*,5*S*)-Ph_2P-Ph-ThrePHOX	BAr_F^-
9	Ir	 n = 1	BAr_F^-
10	Ir	n = 2	BAr_F^-
11	Ir	(*S*)-(*o*Tol)$_2$P-*t*Bu-SimplePHOX	BAr_F^-
12	Ir	(*R*)-Ph_2P-*t*Bu-NeoPHOX	BAr_F^-
13	Ir	(*S*)-Cy_2P-*N*-Ph-*t*Bu-PHIM	BAr_F^-
14	Rh	(*M*)-xyl-BINAP	BF_4^-
15	Rh	(*P*)-BINAP	BF_4^-
16	Rh	(*S*)-SDP	BF_4^-
17	Rh	(*M*)-SegPhos	BF_4^-
18	Rh	(*R,R*)-QuinoxP*	BF_4^-
19	Rh	(*M*)-Cy-SegPhos	BF_4^-
20	Rh	(R_C,S_P)-DuanPhos	BF_4^-
21	Rh	(*P*)-PipPhos	BF_4^-
22	Rh	(*R,R*)-Me-UCAP-DTBM	BF_4^-
23	Rh	(*R,R*)-Me-DuPhos	BF_4^-

Our search began using catalysts **3**−**7** made in situ from commercially available chloro(1,5-cyclooctadiene)rhodium(I) dimer and chiral diphosphine ligands (Table 2, entries 1−5). The amino group in diene **1** was acylated for two reasons in these studies: free amines can act as catalyst poisons to decrease reactivity, and acyl groups can act as anchors for catalysts to increase selectivity. In order to achieve complete conversion to product at low H_2 pressure, the reaction times were increased from the standard procedure developed for Pd/C hydrogenations (Scheme 1). None of these rhodium−phosphine catalysts provided a selective hydrogenation of acetanilide **24** (Table 2, entries 1−5). Only low diastereoselectivity for the unwanted *meso* isomer was achieved, and no enantioselectivity within the C_2 symmetric products was seen. This may have been partly due to the chloride counterion, which is more tightly associated with the cation than the tetrafluoroborate−rhodium catalysts tested at high pressure (compare entries 5 and 8). We started to see encouraging diastereo- and enantioselectivity with rhodium catalysts **14**−**20** at high

dx.doi.org/10.1021/jo3026548 | J. Org. Chem. 2013, 78, 2731−2735

Table 2. Catalysts Screened in Acetanilide 24 Reduction[a]



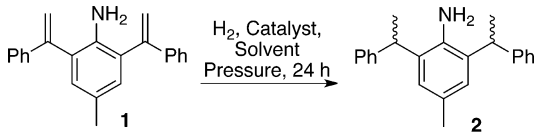
	cat.	*meso*:*RR*:*SS*	solvent
1	**3**	56:22:22	EtOH
2	**4**	60:20:20	EtOH
3	**5**	56:22:22	EtOH
4	**6**	66:17:17	EtOH
5	**7**	60:20:20	EtOH
6	**8**	70:15:15	EtOH
7	**14**	5:1:94	MeTHF
8	**15**	7:93:0	MeTHF
9	**16**	6:1:93	MeTHF
10	**17**	13:0:87	MeTHF
11	**18**	22:4:74	MeOH
12	**19**	24:74:2	MeOH
13	**20**	26:3:72	MeOH

[a]Key: entries 1−6, 100 psi, 40 h; entries 7−13, 500 psi, 40 h.

pressure (Table 2, entries 7−13). The diastereoselectivity was best with catalysts **14**−**16** in 2-methyltetrahydrofuran, and the enantioselectivity of 93−94% was especially encouraging (Table 2, entries 7−9). Iridium catalyst **8** gave increased diastereoselectivity for the *meso* stereoisomer compared to the rhodium catalysts tested at low pressure, but no enantioselectivity was achieved (Table 2, entry 6). None of the iridium catalysts **9**−**13** provided any conversion of **24** to **25**.

We also screened the reduction of aniline **1**. Using iridium-based catalysts **9**−**13**, we continued our search for enantio- and diastereoselectivity at 725 psi (Table 3, entries 1−5). Although

Table 3. Catalysts Screened in Aniline 1 Reduction[a]



	cat.	(*meso*:*R*,*R*:*S*,*S*)	solvent
1	**9**	46:38:16	CH_2Cl_2
2	**10**	46:37:17	CH_2Cl_2
3	**11**	46:52:2	CH_2Cl_2
4	**12**	65:1:34	CH_2Cl_2
5	**13**	91:3:6	CH_2Cl_2
6	**18**	3:3:94	MeOH
7	**20**	1:0:99	MeOH
8	**21**	6:0:94	MeOH
9	**22**	20:74:6	MeOH
10	**23**	31:61:8	MeOH

[a]Key: entries 1−5 at 725 psi, entries 6−10 at 500 psi.

the diastereoselectivity using catalyst **12** was low, the enantioselectivity was about 34:1 in favor of (*S*,*S*)-**2**. Catalyst **13** provided good selectivity for the *meso* diastereomer.

In a final attempt to find conditions to provide both high diastereo- and enantioselectivity, we turned to rhodium-based catalysts (**18**−**23**) prepared in situ from bis(norbornadiene)-rhodium(I) tetrafluoroborate and chiral ligands (Table 3, entries 6−10). In general, the diastereoselectivity was better when the amino group was not acylated. Catalyst **20**, based on the diphosphine ligand (R_C-S_P)-DuanPhos developed by Zhang et al.,[24] provided the highest dr and er for *S*,*S*-**2** of any system tested.

If the two reductions proceed with similar facial selectivity, statistical ratios of the product stereoisomers can be predicted. For example, if each reduction proceeds with 99:1 selectivity for the *S* enantiomer, the ratio of products would be 98.01:0.01:1.98 (*S*,*S*:*R*,*R*:*meso*).[25] The Rh-DuanPhos reduction produced only trace amounts of the *R*,*R* isomer and ∼1% of the *meso* isomer, indicating that each step was ∼99:1 selective.

Upon identifying the Rh-DuanPhos catalyst **20** as the most selective system, we optimized the reaction conditions. We began by probing solvent options. On the basis of solvent studies (Table 4), methanol and ethyl acetate proved to be

Table 4. Solvent Studies with 20 at 500 psi Overnight

solvent	*meso*	*R*,*R*	*S*,*S*
MeOH	1.2	0.2	98.6
EtOH	5.6	0.3	94.1
iPrOH	13.2	0.6	86.2
TFE	33.1	1.4	65.4
DCE	18.5	0.4	81.0
$PhCF_3$	4.9	0.2	94.9
PhCl	6.1	0.3	93.6
CyH	6.4	0.5	93.1
PhMe	6.5	1.8	91.8
EtOAc	3.3	0.2	96.5
iPrOAc	4.0	0.2	95.7
MEK	2.5	0.1	97.4
THF	5.9	0.3	93.8
MeTHF	6.3	0.3	93.4
CPME	5.5	0.3	94.2
DME	3.8	0.2	96.1

viable candidates for the reaction. We chose to proceed with methanol due to the ease of use and solubility of the catalyst. In larger scale-ups, 10 vol % of methylene chloride was employed as a cosolvent to enhance the solubility of diene **1** (see the Experimental Section). To further optimize the system, catalyst loading studies were performed on 0.1 M reactions (Table 5).

Table 5. Loading Studies with 20 at 500 psi Overnight

load (%)	% conversion	*meso*	*R*,*R*	*S*,*S*
5	100.0	1.2	0.2	98.6
2	100.0	3.6	0.3	96.2
1	100.0	4.8	0.5	94.7
0.5	100.0	3.6	0.1	96.3
0.3	99.7	3.1	0.1	96.8
0.2	99.3	3.7	0.1	96.2
0.1	23.1	2.5	0.4	97.0
0.05	9.3	2.5	1.4	96.1

Only 0.2% catalyst loading is needed to effectively reduce the starting material in a reaction at 500 psi overnight. Smaller loadings still exhibit high selectivity but conversion to product is attenuated. In practice, a catalyst loading of 0.5% was employed to ensure that potential catalyst poisons in the substrate lot and reaction vessel would not be as likely to affect the reaction.

The asymmetric hydrogenation of **1** has now been conducted on a 5 g scale, with only small amounts of the *meso*

dx.doi.org/10.1021/jo3026548 | J. Org. Chem. 2013, 78, 2731−2735

diastereomer contaminating the enantiopure product (Figure 2). Aniline **2** can be carried on to the CuIPhEt catalyst using

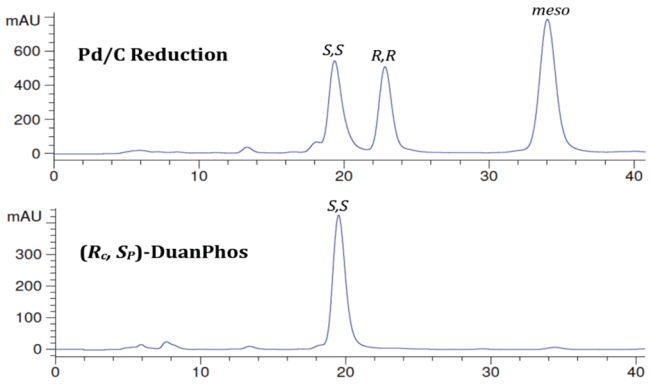


Figure 2. CSP-HPLC of **1**: racemate/meso mixture and *S,S* enantiomer obtained in gram scale reduction.

the published procedure (Scheme 1) without any chromatography.[10] The small amounts of undesired stereoisomers are eliminated during condensation with glyoxal and subsequent manipulations.

CONCLUSION

The asymmetric hydrogenation of 1,1-diaryl-substituted terminal olefins is a challenge, and a highly selective double-asymmetric hydrogenation of functionalized dienes of this type is rare.[23] We found that the Rh-DuanPhos catalyst is highly selective in reducing 2,6-di(1-phenylethenyl)-4-methylaniline (**1**) to provide a key intermediate in the synthesis of the NHC carbenoid CuIPhEt. Through this discovery, CuIPhEt is now attainable through a five-step synthesis in 56% overall yield.

EXPERIMENTAL SECTION

General Methods. All solvents used were reagent grade and were used as received unless otherwise noted. Catalysts **1**−**7** and **14**−**23** were prepared in situ from the requisite ligands and either $[RhCl(COD)]_2$ or $(NBD)_2RhBF_4$, all of which are commercially available and which were used as received. Iridium catalyst **8** was purchased and used as received. Synthesis and characterization of the following catalysts has previously been reported: **9** and **10**,[26] **11**,[27] **12**,[28] and **13**,[29] and **20**.[24,30]

Typical Procedure for Low-Pressure Hydrogenation. The cyclooctadiene rhodium chloride dimer (56.6 μmol) and chiral diphosphine (56.6 μmol), or catalyst **8**, were dissolved in anhydrous ethanol under an inert atmosphere and stirred for 15 min. To the resultant bright orange slurry was added the acetanilide (0.283 mmol). The vessel was purged with hydrogen three times and then pressurized to 100 psi. The solution was heated to 100 °C and shaken for 40 h. The reaction mixture was filtered through a plug of silica and analyzed by CSP-SFC (Chiracel OD-H column with absolute ethanol as modifier).

Typical Procedure for High-Pressure Ir-Catalyzed Hydrogenation. Catalyst **11** (0.9 mg, 0.5 μmol, 1 mol %) was added to a solution of aniline **1** (16.5 mg, 0.05 mmol) in dry CH_2Cl_2 (0.25 mL). The reaction vial was equipped with a magnetic stirrer bar and placed in an autoclave that was pressurized to 725 psi H_2. The reaction mixture was stirred for 24 h at room temperature, after this time, hydrogen was released and the solvent removed under reduced pressure. The mixture was filtered through a plug of silica gel (0.5 × 3 cm) using a mixture of hexane/MTBE (4:1, 2 mL). After evaporation of the solvent, the hydrogenation product (12.8 mg, 0.04 mmol, 77%) was obtained as a yellow oil, together with unreacted starting material. The product ratio, 52:2:46 *RR:SS:meso,* was determined by CSP-HPLC (Chiralpak AD-H, 0.5 mL/min, isocratic, 99:1 heptane/*i*-PrOH).

Typical Procedure for High Pressure Rh-Catalyzed Hydrogenation. In a glovebox with O_2 < 5 ppm, a solution of 0.36 mg (0.95 μmol) of $(NBD)_2RhBF_4$ in 100 μL of 1,2-dichloroethane was added to an 8 × 30 mm vial containing a magnetic stirbar and 0.38 mg (1.0 μmol) of (R_C,S_P)-DuanPhos. The catalyst mixture was stirred for 30 min, and the solvent was removed on a Genevac vacuum centrifuge. A solution of aniline **1** (1.25 mg, 4 μmol) in 100 μL of dry MeOH was then added to the vial. The vial was sealed in a pressure vessel, removed from the glovebox, and pressurized to 500 psi H_2. The vessel was subjected to shaking at 500 rpm at room temperature for 18 h. After this time, hydrogen was released and chiral stationary phase HPLC (Chiralpak OJ-RH 150 × 4.6 mm, 5 μm, 1 mL/min, isocratic 80% CH_3CN/20% 0.1% aq. H_3PO_4, 25 °C) indicated complete conversion to a 98.6:0.2:1.2 mixture of *S,S*:*R,R*:*meso* product isomers.

Large-Scale Reduction Procedure. All large-scale reactions were carried out in Parr 5500 compact mini bench top reactor with the following modifications. The cooling loop was removed and replaced on one side with a Swagelok ball valve with septum and on the other side with a stainless steel plug. The original gas relief valve was modified with Swagelok fittings to become a manifold with three needle valves. The needle valves were designated as ports for N_2, vacuum, or vent. The lower guide bearing that formerly braced the impeller shaft to the cooling loop was reconnected to the dip tube. A 1L Parr High Pressure Buret was connected to the reactor with a high pressure hose. This buret was fitted with valves so that it can be sealed off from both the hydrogen supply cylinder and the reactor. Reactions were performed in a glass insert inside of the stainless steel reactor.

A 25 mL round-bottom flask containing bis(norbornadiene)-rhodium(I) tetrafluoroborate (30 mg, 80 μmol; 0.5 mol % loading) and (S_C, R_P)-DuanPhos (37 mg, 96 μmol) was sealed with a septum and purged with anhydrous nitrogen. Dichloromethane distilled from CaH_2 (6 mL) was added, and the solution was allowed to stir for 15 min. Aniline diene **1** (5 g, 16 mmol) and methanol dried over $MgSO_4$ (55 mL, ∼0.25 M solution) were stirred in a round bottomed flask with stir bar to form a well-distributed slurry before addition to the glass insert for the Parr reactor. The hydrogenation chamber was assembled and then evacuated and flushed five times with nitrogen. The catalyst solution was introduced to the reactor under slight positive pressure of nitrogen via syringe through the ball valve. Upon filling three times and venting the system with hydrogen, the system was pressurized to 500 psi; the buret was closed to the hydrogen cylinder to minimize hydrogen loss in the event of a leak. After vigorously stirring overnight, the reactor was closed to the hydrogen buret, then vented and disassembled. The reaction mixture was filtered through a plug of silica gel (4 × 1.5 cm) and concentrated to yield 4.98 g (98%) as an orange solid. The product mixture was analyzed by chiral stationary phase HPLC (Chiralpak OJ-RH 150 × 2.1 mm, 5 μm, 0.1 mL/min isocratic, 65% CH_3CN/35% 0.1% aq H_3PO_4) indicating complete conversion to a 98:0.2:1.8 mixture of *R,R*:*S,S*:*meso* products.

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of *S,S*-**2** and ^1H ^{13}C and ^{31}P NMR spectra of in situ prepared RhDuanPhos. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: bgawley@uark.edu, michael_shevlin@merck.com, andreas.pfaltz@unibas.ch.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/jo3026548 | J. Org. Chem. 2013, 78, 2731−2735

■ ACKNOWLEDGMENTS

Work in Fayetteville was supported by the National Science Foundation (CHE1011788) and the Arkansas Biosciences Institute; core facilities were supported by the NIH (P30 GM103450). The work in Basel was supported by the Swiss National Science Foundation. We thank Dr. Chris Welch (Merck and Co.) for helpful discussions.

■ REFERENCES

(1) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer-Verlag: Berlin, 2004; Vol. *21*.
(2) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006.
(3) Díez-González; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.
(4) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940.
(5) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: Berlin, 2007.
(6) *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*; Diez-Gonzalez, S., Ed.; Royal Society of Chemistry: London, 2010.
(7) Kühl, O. *Functionalized N-Heterocyclic Carbene Complexes*; Wiley: New York, 2010.
(8) *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Cazin, C. S. J., Ed.; Springer: Berlin, 2011.
(9) Kaur, H.; Zinn, R. K.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157.
(10) Albright, A.; Eddings, D.; Black, R.; Welch, C. J.; Gerasimchuk, N. N.; Gawley, R. E. *J. Org. Chem.* **2011**, *76*, 7341.
(11) Albright, A.; Gawley, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 19680.
(12) Arienti, A.; Bigi, F.; Maggi, R.; Marzi, E.; Moggi, P.; Rastelli, M.; Sartori, G.; Tarantola, F. *Tetrahedron* **1997**, *53*, 3795.
(13) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272.
(14) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.
(15) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513.
(16) Woodmansee, D. H.; Pfaltz, A. *Chem. Commun.* **2011**, *47*, 7912.
(17) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761.
(18) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241.
(19) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445.
(20) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282.
(21) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344.
(22) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998.
(23) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881.
(24) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, *2005*, 646.
(25) $(0.99)^2$:$(0.01)^2$:$2(0.99 \times 0.01)$.
(26) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194.
(27) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023.
(28) Schrems, M. G.; Pfaltz, A. *Chem. Commun.* **2009**, *0*, 6210.
(29) Menges, F. University of Basel, 2004, http://edoc.unibas.ch/diss/DissB_6766.
(30) Zigterman, J. L.; Woo, J. C. S.; Walker, S. D.; Tedrow, J. S.; Borths, C. J.; Bunel, E. E.; Faul, M. M. *J. Org. Chem.* **2007**, *72*, 8870.