Published in final edited form as:

J Org Chem. 2013 March 15; 78(6): 2731–2735. doi:10.1021/jo3026548.

A Double Asymmetric Hydrogenation Strategy for the Reduction of 1,1-Diaryl Olefins Applied to an Improved Synthesis of CuIPhEt, a C₂-Symmetric N-Heterocyclic Carbenoid

Elizabeth Spahn^a, Abigail Albright^a, Michael Shevlin^{b,*}, Larissa Pauli^c, Andreas Pfaltz^{c,*}, and Robert E. Gawley^{a,*}

^aDepartment of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas, 72701, USA ^bDepartment of Process Chemistry, Merck and Co., Inc., P. O. Box 2000, Rahway, New Jersey, 07065, USA ^cDepartment of Chemistry, University of Basel, St. Johannis-Ring 19, CH-4056 Basel, Switzerland

Abstract

A library of iridium and rhodium phosphine catalysts have been screened for the double asymmetric hydrogenation of 2,6-di-(1-phenylethenyl)-4-methyl aniline to produce the C₂-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 4 step asymmetric synthesis of the C₂-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-ylidene (IPr) ligand⁹ 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 minutes 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 minutes at room temperature.

*bgawley@uark.edu, michael_shevlin@merck.com, andreas.pfaltz@unibas.ch.

Supporting Information. ¹H and ¹³C NMR spectra of *S,S*-2 and ¹H ¹³C and ³¹P NMR spectra of *in situ*-prepared Rh DuanPhos. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Especially noteworthy is the hydrosilylation of 2-butanone and 3-heptanone, which proceeded in 98:2 and 95:5 er, respectively.

In our first synthesis of CuIPhEt (Scheme 1),¹⁰ we used Sartori's procedure¹² 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 3 steps. X-Ray crystallography revealed a beautiful chiral pocket surrounding the copper atom (Figure 1). Because of the excellent selectivity exhibited by CuIPhEt in 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 selectivities 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 coworkers 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 H₂. Under these conditions a range of 2-aryl-1-butenes was hydrogenated with high enantioselectivities 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.

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 coworkers (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 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).

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 decreasing reactivity and acyl groups can act as anchors for catalysts increasing selectivity. In order to achieve complete conversion to product at low H₂ 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 C2 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 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 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. Based on solvent studies (Table 4), methanol and ethyl acetate proved to be viable candidates for the reaction. We chose to proceed with methanol due to ease of use and solubility of the catalyst. In larger scale-ups, 10 vol% of methylene chloride was employed as a co-solvent to enhance the solubility of diene **1** (see experimental section). To further optimize the system, catalyst loading studies were performed on 0.1 M reactions (Table 5). 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 gram scale, with only small amounts of the *meso* diastereomer contaminating the enantiopure product (Figure 2). Aniline **2** can be carried on to the CuI^{PhEt} catalyst using the published procedure (Scheme

1) without any chromatography.¹⁰ The small amounts of undesired stereoisomers are eliminated during condensation with glyoxal and subsequent crystallizations.

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 are rare.²³ We found that the Rh-DuanPhos catalyst is highly selective in reducing 2,6-di-(1-phenylethenyl)-4-methyl aniline (**1**) to provide a key intermediate in the synthesis of the NHC carbenoid CuI^{Ph}Et. Through this discovery, CuI^{Ph}Et is now attainable through a 5 step synthesis in 56% overall yield.

Experimental

General

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)₂RhBF₄, 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 μ mol) and chiral diphosphine (56.6 μ mol), 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, then pressurized to 100 psi. The solution was heated to 100 °C and shaken for 40 hrs. 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 μ mol, 1 mol%) was added to a solution of aniline **1** (16.5 mg, 0.05 mmol) in dry CH₂Cl₂ (0.25 mL). The reaction vial was equipped with a magnetic stirrer bar and placed in an autoclave that was pressurized to 725 psi H₂. The reaction mixture was stirred for 24 hours 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 $\times$ 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 O₂ < 5 ppm, a solution of 0.36 mg (0.95 μ mol) (NBD)₂RhBF₄ in 100 μ L 1,2-dichloroethane was added to a 8 $\times$ 30 mm vial containing a magnetic stirbar and 0.38 mg (1.0 μ mol) 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 μ mol) in 100 μ L 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 H₂. The vessel was subjected to shaking at 500 rpm at room temperature for 18 hours. After this time, hydrogen was released and chiral stationary phase HPLC (Chiralpak OJ-RH 150 $\times$ 4.6 mm, 5 μ m, 1 mL /

min, isocratic 80% CH₃CN / 20% 0.1% aq. H₃PO₄, 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 3 needle valves. The needle valves were designated as ports for N₂, 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 Burette was connected to the reactor with a high pressure hose. This burette 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 CaH₂ (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 MgSO₄ (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, 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 thrice filling and venting the system with hydrogen, the system was pressurized to 500 psi; the burette 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 burette, 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% CH₃CN / 35% 0.1% aq. H₃PO₄) indicating complete conversion to a 98:0.2:1.8 mixture of *R,R:S,S:meso* products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Work in Fayetteville was supported by the US 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.

Notes and References

- (1). Glorius, F., editor. N-Heterocyclic carbenes in transition metal catalysis. Vol. Vol. 21. Springer-Verlag; Berlin: 2004.
- (2). Nolan, SP., editor. N-Heterocyclic carbenes in synthesis. Wiley-VCH; Weinheim: 2006.
- (3). Díez-González, Marion N, Nolan SP. Chem. Rev. 2009; 109:3612. [PubMed: 19588961]
- (4). Dröge T, Glorius F. Angew. Chem. Int. Ed. 2010; 49:6940.
- (5). Glorius, F., editor. N-Heterocyclic carbenes in transition metal catalysis. Springer; Berlin: 2007.

- (6). Diez-Gonzalez, S., editor. N-Heterocyclic Carbenes: From laboratory curiosities to efficient synthetic tools. Royal Society of Chemistry; 2010.
- (7). Köhl, O. Functionalized N-Heterocyclic Carbene Complexes. Wiley; 2010.
- (8). Cazin, CSJ., editor. N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis. Springer; Berlin: 2011.
- (9). Kaur H, Zinn RK, Nolan SP. Organometallics. 2004; 23:1157.
- (10). Albright A, Eddings D, Black R, Welch CJ, Gerasimchuk NN, Gawley RE. J. Org. Chem. 2011; 76:7341. [PubMed: 21823580]
- (11). Albright A, Gawley RE. J. Am. Chem. Soc. 2011; 133:19680. [PubMed: 22074559]
- (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. [PubMed: 16159153]
- (14). Roseblade SJ, Pfaltz A. Acc. Chem. Res. 2007; 40:1402. [PubMed: 17672517]
- (15). Church TL, Andersson PG. Coordination Chemistry Reviews. 2008; 252:513.
- (16). Woodmansee DH, Pfaltz A. Chem. Commun. 2011; 47:7912.
- (17). Conticello VP, Brard L, Giardello MA, Tsuji Y, Sabat M, Stern CL, Marks TJ. J. Am. Chem. Soc. 1992; 114:2761.
- (18). Giardello MA, Conticello VP, Brard L, Gagne MR, Marks TJ. 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 SP, Pfaltz A. Adv. Synth. Catal. 2005; 347:282.
- (21). Mazuela J, Verendel JJ, Coll M, Schäffner B, Börner A, Andersson PG, Pàmies O, Diéguez M. J. Am. Chem. Soc. 2009; 131:12344. [PubMed: 19658416]
- (22). Knowles WS. Angew. Chem. Int. Ed. 2002; 41:1998.
- (23). Wang X, Guram A, Caille S, Hu J, Preston JP, Ronk M, Walker S. Org. Lett. 2011; 13:1881. [PubMed: 21384895]
- (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 SP, Pfaltz A. Angew. Chem. Int. Ed. 2006; 45:5194.
- (27). Smidt SP, Menges F, Pfaltz A. Org. Lett. 2004; 6:2023. [PubMed: 15176809]
- (28). Schrems MG, Pfaltz A. Chem. Commun. 2009; 0:6210.
- (29). Menges, F. University of Basel. 2004. http://edoc.unibas.ch/diss/DissB_6766
- (30). Zigterman JL, Woo JCS, Walker SD, Tedrow JS, Borths CJ, Bunel EE, Faul MM. J. Org. Chem. 2007; 72:8870. [PubMed: 17927253]

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

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

Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Catalyst library. See the SI for structures

Catalyst	M+	Ligand	X ⁻
3	Rh	(<i>S,S</i>)-DIOP	Cl ⁻
4	Rh	(<i>R,R</i>)-Chiraphos	Cl ⁻
5	Rh	(<i>R,R</i>)-Skewphos	Cl ⁻
6	Rh	(<i>R,R</i>)-Norphos	Cl ⁻
7	Rh	(<i>M</i>)-BINAP	Cl ⁻
8	Ir	(4 <i>S</i> ,5 <i>S</i>)-Ph ₂ P Ph-ThrePHOX	BArF ⁻
9 10	Ir Ir	$n = 1$ $n = 2$	BArF ⁻ BArF ⁻
11	Ir	(<i>S</i>)-(oTol) ₂ P tBu- SimplePHOX	BArF ⁻
12	Ir	(<i>R</i>)-Ph ₂ P-tBu- NeoPHOX	BArF ⁻
13	Ir	(<i>S</i>)-Cy ₂ P- <i>N</i> -Ph- tBu-PHIM	BArF ⁻
14	Rh	(<i>M</i>)-xyl-BINAP	BF ₄ ⁻
15	Rh	(<i>P</i>)-BINAP	BF ₄ ⁻
16	Rh	(<i>S</i>)-SDP	BF ₄ ⁻
17	Rh	(<i>M</i>)-SegPhos	BF ₄ ⁻
18	Rh	(<i>R,R</i>)-QuinoxP*	BF ₄ ⁻
19	Rh	(<i>M</i>)-Cy- SegPhos	BF ₄ ⁻
20	Rh	(<i>R_C</i> , <i>S_P</i>)- DuanPhos	BF ₄ ⁻
21	Rh	(<i>P</i>)-PipPhos	BF ₄ ⁻
22	Rh	(<i>R,R</i>)-Me- UCAP-DTBM	BF ₄ ⁻
23	Rh	(<i>R,R</i>)-Me- DuPhos	BF ₄ ⁻

Table 2

Catalysts screened in acetanilide reduction. Entries 1-6, 100 psi, 40 h; entries 7-13, 500 psi, 40 h

	Cat.	<i>meso:RR:SS</i>	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

Table 3Catalysts screened in aniline **1** reduction. Entries 1-5 at 725 psi, entries 6-10 at 500 psi

	Cat.	(<i>meso</i> : <i>R,R</i> : <i>S,S</i>)	Solvent
1	9	46 : 38 : 16	CH ₂ Cl ₂
2	10	46 : 37 : 17	CH ₂ Cl ₂
3	11	46 : 52 : 2	CH ₂ Cl ₂
4	12	65 : 1 : 34	CH ₂ Cl ₂
5	13	91 : 3 : 6	CH ₂ Cl 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

Table 4Solvent studies with **20** at 500 psi overnight

Solvent	<i>meso</i>	<i>R,R</i>	<i>S,S</i>
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

Table 5

Loading studies with 20 at 500 psi overnight

Load %	Conversion	<i>meso</i>	<i>R,R</i>	<i>S,S</i>
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
.05%	9.3	2.5	1.4	96.1