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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Catalytic, Asymmetric, and Stereodivergent Synthesis of Non-Symmetric β,β-Diaryl-α-Amino Acids

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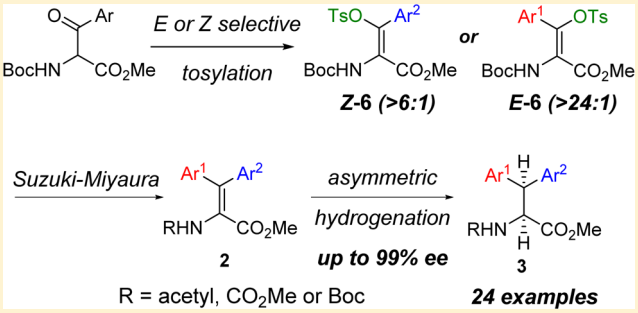
Supporting Information

ABSTRACT: We report a concise, enantio- and diastereoselective route to novel nonsymmetrically substituted *N*-protected β,β-diaryl-α-amino acids and esters, through the asymmetric hydrogenation of tetrasubstituted olefins, some of the most challenging examples in the field. Stereoselective generation of an *E*- or *Z*-enol tosylate, when combined with stereoretentive Suzuki-Miyaura cross-coupling and enantioselective hydrogenation catalyzed by $(NBD)_2RhBF_4$ and a Josiphos ligand, allows for full control over the two vicinal stereogenic centers. High yields and excellent enantioselectivities (up to 99% ee) were obtained for a variety of *N*-acetyl, *N*-methoxycarbonyl, and *N*-Boc β,β-diaryldehydroamino acids, containing a diverse and previously unreported series of heterocyclic and aryl substituted groups (24 examples) and allowing access to all four stereoisomers of these valuable building blocks.



INTRODUCTION

The β,β-diarylalanine structural motif is an important pharmacophore in molecular agents that target many diseases, including atherosclerosis,[1] cancer,[2] diabetes insipidus,[3] diabetes mellitus type 2,[4] HIV,[5] and thrombosis[6] (Figure 1). Additionally, this

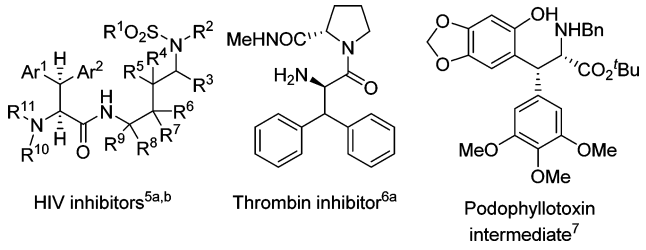
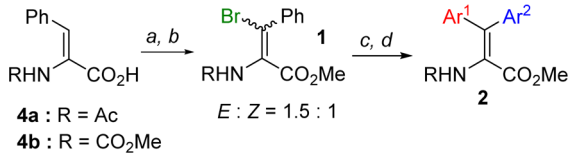


Figure 1. Representative β,β-diarylalanine derivatives.

structural class appears in synthetic intermediates in natural product synthesis.[7] Due to this broad utility, β,β-diarylalanine derivatives have attracted considerable interest and a number of approaches for synthesizing derivatives with two identical β-aryl substituents have been reported.[8] The synthesis of β,β-diarylalanines, where both β-aryl substituents are nonidentical represents a considerable synthetic challenge due to the formation of a second, vicinal stereogenic center. These compounds have been synthesized by diastereoselective S_N1 reactions on phenylalanine derivatives,[9] opening of aziridines,[10] alkylations employing a chiral auxiliary,[11] alkylation of glycine derivatives[12] and nitroacrylates[13] in the presence of a chiral catalyst, and

Scheme 1. Synthesis of *N*-Acetyl and *N*-Methoxycarbonyl Dehydroamino Acids via Vinyl Bromides[a]



[a]*Conditions:* (a) 1.05 equiv $SOCl_2$, 2.1 equiv Et_3N, 10 equiv MeOH, DCM, 0 °C; (b) 1.1 equiv NBS, 1.1 equiv Et_3N, DCM, 88%; (c) Chromatographic separation; and (d) 15 mol % $Pd(OAc)_2$, 15 mol % DavePhos, 1.3 equiv $ArB(OH)_2$, 2.5 equiv K_3PO_4—H_2O, THF/H_2O, 70 °C.

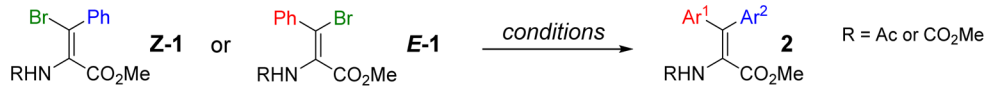
tandem Aza-Darzens/ring opening reactions in the presence of a chiral reagent.[14] Recently, palladium-catalyzed C—H functionalizations of alanine derivatives have been reported under the direction of auxiliary[15] or ligand control.[16] Despite all these efforts, the requirement for exotic protecting groups, directing groups or ligands, stoichiometric silver, high palladium catalyst loadings, expensive chirality sources or narrow substrate scope limits their practicality.

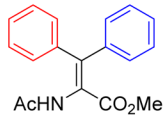
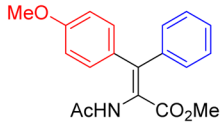
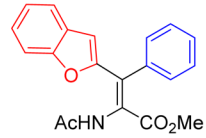
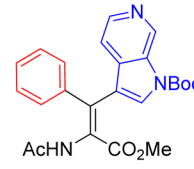
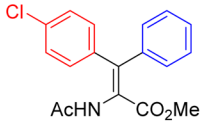
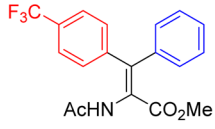
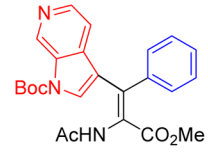
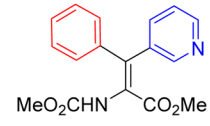
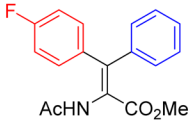
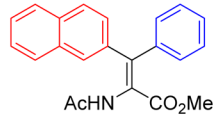
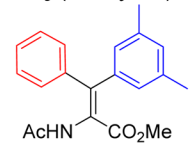
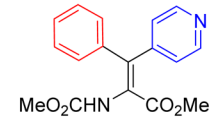
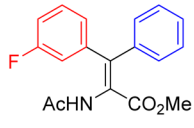
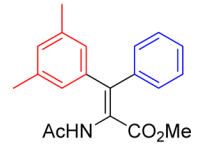
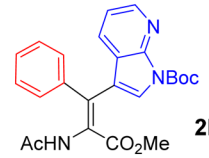
During the course of our research to support discovery and clinical evaluation of a candidate molecule, we required rapid, *modular* access to enantioenriched, *differentially substituted* β,β-diarylalanine derivatives. We envisioned that the synthesis of differentially substituted dehydro-β,β-diarylalanine derivatives

Received: November 25, 2014
Published: December 18, 2014

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006

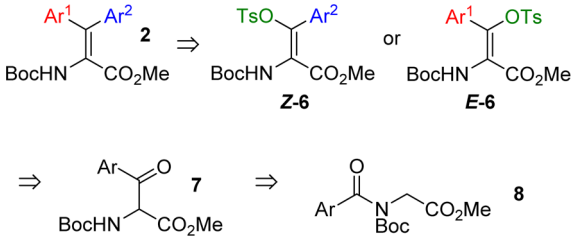
Table 1. Suzuki-Miyaura Cross-Coupling Results with *E*- and *Z*-Vinyl Bromides



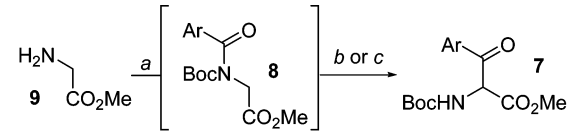
Entry[a]	Product[b]	Entry[a]	Product[b]	Entry[a]	Product[b]	Entry[a]	Product[b]
1[c]	 **2a** (49% yield)	5[c]	 **2e** (86% yield)	9[c]	 **2i** (63% yield)	13[d,e]	 **2m** (34% yield)
2[c]	 **2b** (65% yield)	6[c]	 **2f** (64% yield)	10[c,e]	 **2j** (68% yield)	14[f]	 **2n** (20% yield)[g]
3[c]	 **2c** (73% yield)	7[c]	 **2g** (69% yield)	11[d]	 **2k** (63% yield)	15[f]	 **2o** (39% yield)[h]
4[c]	 **2d** (65% yield)	8[c]	 **2h** (48% yield)	12[d]	 **2l** (48% yield)		

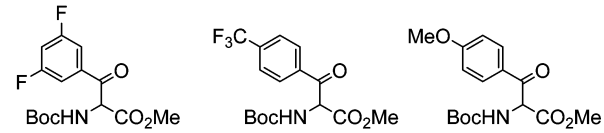
Conditions. [a]15 mol % $Pd(OAc)_2$, 15 mol % DavePhos, 1.3 equiv $ArB(OH)_2$, 2.5 equiv K_3PO_4–H_2O, THF/H_2O, 70 °C. [b]Isolated yield. [c]Isomer *Z*-**1** was used. [d]Isomer *E*-**1** was used. [e]15 mol % dppf used. [f]*E*/*Z* mixture of **1** was used. [g]84% of a 1:3 *E*/*Z* mixture of isomers was obtained and then separated. [h]64% of a 3:2 *E*/*Z* mixture of isomers was obtained and then separated.

Scheme 2. Retrosynthetic Analysis



Scheme 3. One-Pot Telescoped β-Ketoester Synthesis[a]





7a (77% yield)[a,b] **7b** (81% yield)[a,b] **7c** (75% yield)[a,c]

[a]*Conditions:* (a) Et_3N, ArCOCl, 2-MeTHF, <10 °C; Boc_2O, DMAP, 2-MeTHF, 20 °C; (b) *t*-BuOK, 2-MeTHF, <10 °C; and (c) LHMDS, DMPU, 2-MeTHF, −78 °C. Yields are of isolated products **7** obtained via direct crystallization.

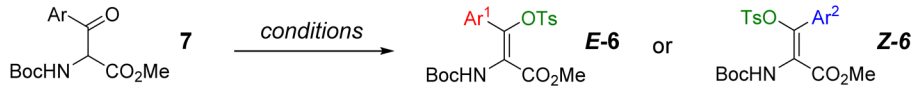
followed by asymmetric hydrogenation[17,18] could provide rapid access to any stereoisomer of a given β,β-diarylalanine derivatives in high optical purity. Surprisingly, the asymmetric hydrogenation of such nonsymmetrically tetrasubstituted olefins has not been previously reported.[19] Herein, we report our results in (1) identifying a catalyst system that can enantioselectively reduce such highly congested systems without loss of olefin geometric integrity; and (2) stereoselectively configuring the *E*- or *Z*-double bond geometry of the hydrogenation substrates from a common synthetic precursor.

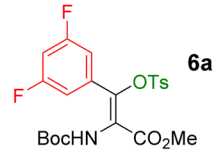
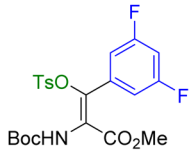
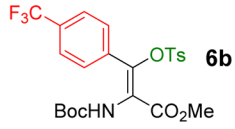
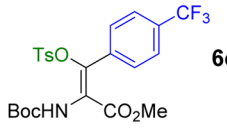
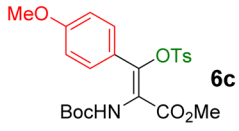
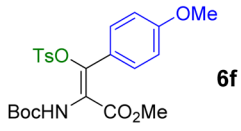
RESULTS AND DISCUSSION

Preparation of *N*-Acetyl and *N*-Methoxycarbonyl Protected Dehydroamino Acids. Our study began with targeting nonsymmetric *N*-acetyl and *N*-methylcarbamate protected β,β-diarylamino acids. Initially, dehydroamino acids **2** were prepared in 3 steps from commercially available substituted propenoic acid **4a** or **4b** (Scheme 1). Esterification under standard conditions and treatment with NBS with triethylamine gave the corresponding β-bromo-β-substituted dehydroamino esters **1** in 88% combined yield as a 1.5:1 mixture of *E*- and *Z*-isomers.[20] The isomers were separable by flash chromatography and could be individually coupled under Suzuki-Miyaura conditions with commercially available arylboronic acids. A catalyst complex of $Pd(OAc)_2$ and DavePhos[21,22] provided alkenes **2** in yields ranging from 45 to 89% (Table 1). Alternatively, in some instances, the *E*/*Z* mixture of **1** could be directly coupled

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999–1006

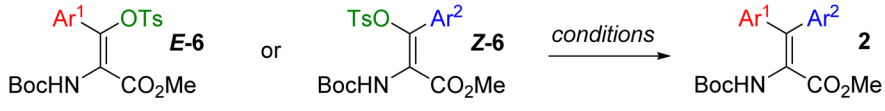
Table 2. Stereocontrolled *Z*- and *E*-Enol Tosylate Synthesis

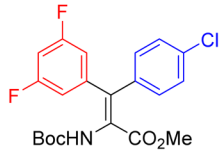
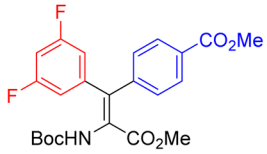
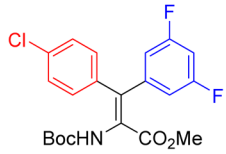
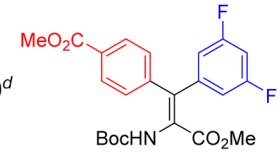
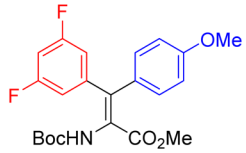
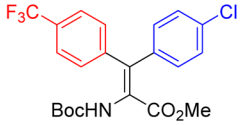
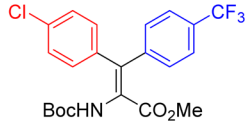
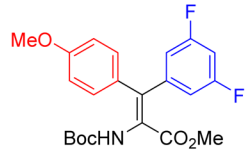
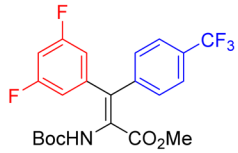
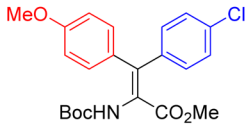
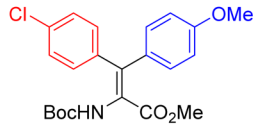
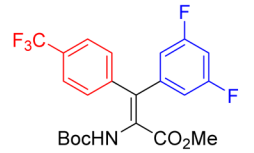


Entry	Product	*E*:*Z*[e]	Yield (%)[f]	Entry	Product	*E*:*Z*[e]	Yield (%)[f]
1[a]	 **6a**	45 : 1	50	4[b]	 **6d**	1 : 9	79
2[a]	 **6b**	24 : 1	84	5[b]	 **6e**	1 : 6	86
3[c]	 **6c**	99 : 1	58	6[d]	 **6f**	1 : 7	78

Conditions. [a]LDA, Ts_2O, THF, −50 °C. [b]Et_3N, Ts_2O, CH_3CN, 25 °C. [c]LHMDS, Ts_2O, THF, −50 °C. [d]iPr_2NEt, Ts_2O, CH_3CN, 25 °C. [e]*E*/Z ratios determined by HPLC of unpurified reaction mixtures. [f]Yields are of isolated products obtained via direct crystallization.

Table 3. Suzuki-Miyaura Cross-Coupling Results with *E*- and *Z*-Tosylates



Entry[a]	Product[b]	Entry[a]	Product[b]	Entry[a]	Product[b]	Entry[a]	Product[b]
1[c]	 **2p** (56% yield)	4[c]	 **2s** (89% yield)	7[d]	 **2v** (79% yield)	10[d]	 **2y** (77% yield)
2[c]	 **2q** (71% yield)	5[c]	 **2t** (98% yield)	8[d]	 **2w** (94% yield)	11[d]	 **2z** (65% yield)
3[c]	 **2r** (83% yield)	6[c]	 **2u** (82% yield)	9[d]	 **2x** (95% yield)	12[d]	 **2aa** (78% yield)

Conditions. [a]1.01 equiv $ArB(OH)_2$, $Pd(OAc)_2$ (0.5 mol %), dppb (1.1 mol %), 1.0 equiv K_3PO_4, 2-MeTHF, H_2O, 70 °C. [b]Yields are of isolated products obtained via crystallization. [c]Isomer *E*-**6** was used. [d]Isomer *Z*-**6** was used.

and the product isomers separated subsequently by flash chromatography.[23] Although this approach allowed for an expedient preparation of a variety of dehydroamino acids **2a**−**2o** containing heterocyclic and substituted aryl groups primed for asymmetric reduction, it suffered in the ability to control the *E*/*Z* geometry of the tetrasubstituted alkene. We sought to address this limitation and thereby increase the overall synthetic efficiency. Moreover, a more readily removable nitrogen protecting group was highly desirable to increase the utility of the resulting *β*,*β*-diarylamino acid ester synthons.

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006

Preparation of *N*-Boc Protected Dehydroamino Acids. In our revised analysis, we focused on the preparation of racemic *α*-*N*-Boc-amino-*β*-ketoesters **7**, which we expected to be readily available by rearrangement of simple *N*-acylated-*N*-Boc glycine methyl ester derivatives **8** (Scheme 2). In the forward sense, sterecontrolled generation of either the *Z*-enol tosylate or the *E*-isomer from **7**, followed by stereoretentive Suzuki-Miyaura cross-coupling with commercially available aryl boronic acids would afford either tetrasubstituted double bond isomer. Early on, we recognized that even if enolization (*E* vs *Z*) of **7** were limited to accessing just one of the two possible enol tosylates selectively, reversing the order in which the aryl groups were introduced would still potentially allow for optional selection of the *β*-amino acid stereogenic center.

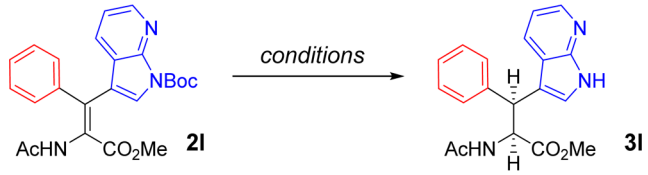
We began with the preparation of the *β*-ketoesters **7a−c** from commercially available glycine methyl ester **9** (Scheme 3). A telescoped through process for *N*-benzoylation, *N*-Boc protection, followed by base mediated aza-Chan N → C rearrangement was developed and thereby avoided the need to isolate the intermediates **8**.[24] Yields were good for the acid chlorides evaluated (75−81%) and the products **7a−c** were all crystalline solids. The rearrangement of the electron rich intermediate **8c** (Ar = 4-methoxyphenyl) was unsatisfactory using *t*BuOK and LHMDS was the preferred base in this instance.

Next we evaluated our ability to control the enolization selectivity of *α*-*N*-Boc-amino-*β*-ketoesters **7a−c**. We focused on the preparation of their enol tosylate derivatives due to the documented use in Suzuki-Miyaura cross-couplings[25] and an expectation of advantageous chemical stability and crystallinity. Following screening of conditions using substrate **7a**, two complementary reaction protocols emerged. Specifically, a tertiary amine base (Et_3N or iPr_2NEt) with Ts_2O in CH_3CN was found to be *Z*-selective (≥6:1) while the use of LDA or LHMDS with Ts_2O in THF favored the *E*-isomer preferentially (≥24:1) (Table 2). Application of these conditions to **7a−c** afforded *E*- and *Z*-enol tosylates **6a−c** and **6d−f** in 50−86% isolated yield by direct crystallization and with >99% geometric purity.[26,27] With the enol tosylates in hand, attention turned to their Suzuki-Miyaura coupling reactions with a variety of commercially available arylboronic acids.

Early studies of the coupling of *Z*-tosylate **6d** with 4-chlorophenylboronic acid indicated geometrical leakage was a major issue such that a mixture (up to 80% of the isomer!) of the two possible tetrasubstituted double bond isomeric products could result. Subsequent hydrogenation would afford an undesirable mixture at the *β*-stereogenic center. Screening of phosphine ligand, Pd precatalyst, base and solvent in tandem with DoE optimization identified the use of $Pd(OAc)_2$ (0.5 mol %), 1,4-bis(diphenylphosphino) butane (dppb) (1.1 mol %) and K_3PO_4 (100 mol %) in 2-MeTHF (10 vol) and water (5 vol) as suppressing this undesired scrambling.[28,29] Under these preferred conditions, scrambling was limited to just 7% and crystalline product **2v** could be directly isolated from *i*PrOH and water in 79% yield with >99:1 *E*/*Z* purity. A variety of further dehydroamino acids **2w−2aa** were then accessed in good to excellent yields using these conditions (65−95%) (Table 3, entries 7−12).

In all of the other *Z*-tosylate couplings, 6% or less of the undesired olefin isomer was formed and the desired products can be upgraded by direct crystallization. While a full understanding of the mechanism for loss of geometric fidelity has not been delineated at this time, some observations are possible. Control reactions with dppb, K_3PO_4 and 4-$ClC_6H_4B(OH)_2$ present but in the absence of $Pd(OAc)_2$ indicate no isomerization or decomposition of **6d** after 3 h at 70 °C. In addition, the *Z*/*E* ratio of Suzuki-Miyaura product mixtures were stable to prolonged aging. Thus, Pd appears to be required for scrambling and isomerization is not a simple result of base promoted conjugate addition and elimination to the acrylate starting materials or products. In contrast to the *Z*-tosylates, no double bond scrambling was observed in the Suzuki-Miyaura coupling of the *E*-tosylate counterparts **6a−c** using the previously optimized conditions and the coupling reactions were faster. Access to a range of dehydroamino acids **2p−2u** was possible with good to excellent isolated yields (56−98%) (Table 3, entries 1−6).

Table 4. Ligand Screen for the Enantioselective Rh-Catalyzed Hydrogenation of Substrate 2l



entry[a]	loading[b]	ligand[c]	conversion[d]	%ee[d]
1	20	T021−2	81	85
2	20	T025−2	96	93
3	20	W022−1	97	92[e]
4	20	W016−1	96	92[e]
5	20	W023−1	100	95[e]
6	20	W017−1	95	96[e]
7	20	J212−1	100	80
8	20	J012−1	100	88
9	20	J002−1	97	93
10	20	J014−1	99	94
11	20	J210−1	100	96
12	20	J011−1	98	97
13[f]	10	J011−1	100	97
14[f]	5	J011−1	100	97
15[f]	2	J011−1	95	96
16[f]	1	J011−1	69	93

[a]*Conditions*: $(NBD)_2RhBF_4$, MeOH, 0.02M, 500 psi H_2, 40 °C. [b]Mol% Rh. A ratio of 1.05:1 Ligand/Rh was used. [c]See Figure 2 for ligand structures. [d]As determined by chiral SFC at 210 nm. Boc deprotection of the aza-indole was observed during the screen. The conversion were determined by fully deprotecting the products at the end of the reaction. Absolute configuration (*2S*, *3S*) unless otherwise stated. [e](*2R*, *3R*). [f]0.1 M concentration was used.

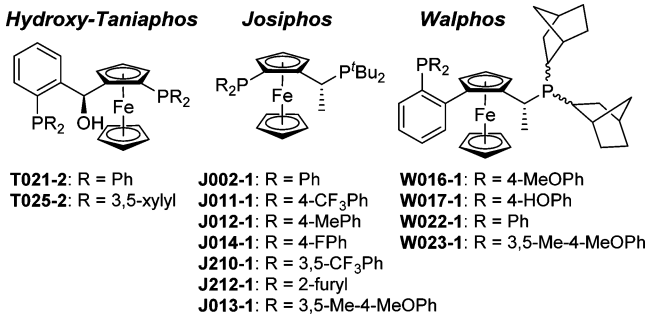
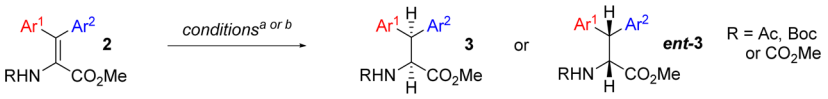


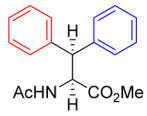
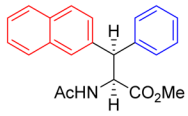
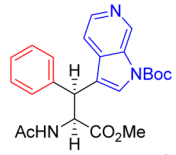
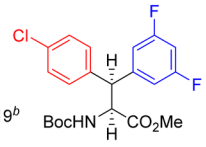
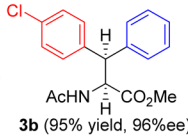
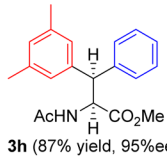
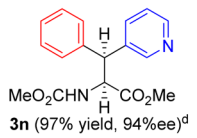
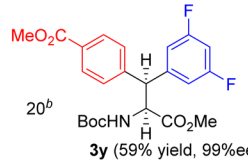
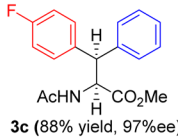
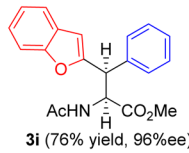
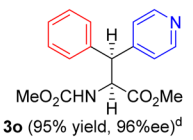
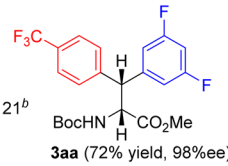
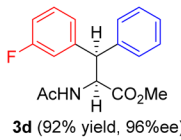
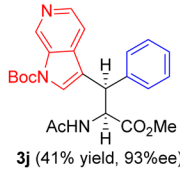
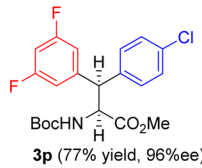
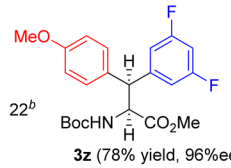
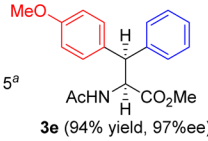
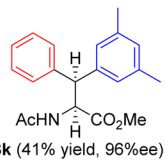
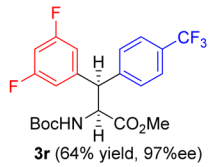
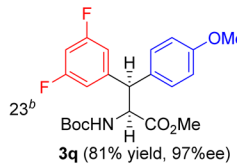
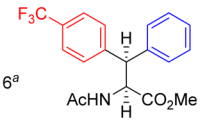
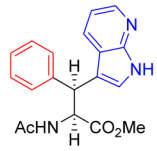
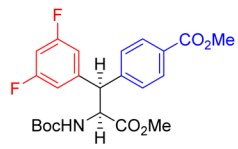
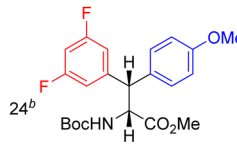
Figure 2. Ligands used in hydrogenation screening.

Asymmetric Hydrogenation. With dehydroamino acids in hand, we began our investigation of the asymmetric hydrogenation using *N*-acetyl protected alkene **2l** as a model substrate. While ruthenium and iridium catalysts gave poor reactivity, rhodium catalysts gave good reactivity and selectivity using

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006

Table 5. Enantioselective Hydrogenation of *N*-Ac, *N*-CO_2Me, and *N*-Boc Protected *β*,*β*-Diaryl Dehydroamino Acids



Entry	Product	Entry	Product	Entry	Product	Entry	Product
1[a]	 **3a** (94% yield, 97%ee)	7[a]	 **3g** (81% yield, 96%ee)	13[a]	 **3m** (68% yield, 88%ee)[g]	19[b]	 **3v** (88% yield, 97%ee)
2[a]	 **3b** (95% yield, 96%ee)	8[a]	 **3h** (87% yield, 95%ee)	14[a]	 **3n** (97% yield, 94%ee)[d]	20[b]	 **3y** (59% yield, 99%ee)
3[a]	 **3c** (88% yield, 97%ee)	9[a]	 **3i** (76% yield, 96%ee)	15[a]	 **3o** (95% yield, 96%ee)[d]	21[b]	 **3aa** (72% yield, 98%ee)[c]
4[a]	 **3d** (92% yield, 96%ee)	10[a]	 **3j** (41% yield, 93%ee)[d,e]	16[b]	 **3p** (77% yield, 96%ee)	22[b]	 **3z** (78% yield, 96%ee)
5[a]	 **3e** (94% yield, 97%ee)	11[a]	 **3k** (41% yield, 96%ee)	17[b]	 **3r** (64% yield, 97%ee)	23[b]	 **3q** (81% yield, 97%ee)
6[a]	 **3f** (87% yield, 95%ee)	12[a]	 **3l** (85% yield, 94%ee)[d,f]	18[b]	 **3s** (71% yield, 92%ee)	24[b]	 **ent-3q** (72% yield, 99%ee)[c]

[a]*Conditions:* 5 mol % $(NBD)_2RhBF_4$, 5.25 mol % J011−1, 400 psi H_2, MeOH, 0.1 M, 25 °C. [b]*Conditions:* 10 mol % $(NBD)_2RhBF_4$, 10.5 mol % J212−1, 120 psi H_2, *i*PrOH, 0.5M, 80 °C, 22 h. Enantioselectivities were determined by chiral stationary phase HPLC of unpurified reaction mixtures. Yields are of isolated products obtained via chromatography or crystallization and are unoptimized. [c]J212−2 used instead of J212−1. [d]1.2 equiv HBF_4·OEt_2 was added. [e]100% conversion to a mixture of **3j** and partial Boc deprotection of the aza-indole was observed (~1:1.5). Only yield of **3j** is reported. [f]100% conversion to a mixture of **3l** and partial Boc protected aza-indole was observed. The mixture was fully deprotected and yield of **3l** is reported. [g]100% conversion to a mixture of **3m** and partial Boc deprotection of the aza-indole was observed. Only yield of **3m** is reported.

$(NBD)_2RhBF_4$ as the precatalyst in MeOH under 500 psi H_2 at 40 °C (Table 4).[30] Over 150 ligands were tested and the ligands giving good conversion to product with excellent selectivity were C_1-symmetric planar chiral ferrocenes (Figure 2). Aryl-substituted hydroxy-Taniaphos[31] and aryl, norbornyl-substituted Walphos ligands[32] gave selectivities up to 96% ee (Table 4, entries 1−6). However, since these ligands have limited commercial availability, we turned to the related and more available Josiphos ligand family. Gratifyingly, aryl, *tert*-butyl substituted Josiphos ligands[33] gave high levels of activity and selectivity (Table 4, entries 7−12), with 4-trifluoromethylphenyl Josiphos ligand J011−1 giving 97% ee (Table 4, entry 12). It is interesting to note that while the Walphos and Josiphos ligands have the same sense of chirality and similarly bulky alkyl substitution, the phenyl spacer in the Walphos ligands results in an inversion of enantioselectivity compared to Josiphos (Table 4, entries 3−6). An examination of catalyst loading with the ligand J011−1 revealed that 5 mol % gave complete conversion and high selectivity, while further reductions of catalyst loading led to reduced activity and enantioselectivity (Table 4, entries 13−16).

With optimized conditions in hand, a variety of *N*-acetyl and *N*-methoxycarbonyl *β*,*β*-diaryl dehydroamino acids **2a**−**2o** were hydrogenated (Table 5). All the substrates tested afforded excellent enantioselectivities (88−97%) independent of whether the substituents on the phenyl ring were electron donating or electron withdrawing (Table 5, entries 1−8).[34] The hydrogenation worked equally well with *E*- or *Z*-alkenes (Table 5, entry 10 vs 13) and gratifyingly, in addition to substituted phenyl

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006

rings, benzofurans, azaindoles and pyridines were also tolerated affording high enantioselectivities (Table 5, entries 9, 10, 12−15). Furthermore, methoxycarbonyl-protected substrates also gave good results (Table 5, entries 14−15). In all cases, no diastereomeric products were observed, indicating that there was no isomerization of the olefin during the hydrogenation.[35]

We next turned our attention to *N*-Boc protected dehydroamino acid substrates **2p**−**2aa**. We expected that asymmetric hydrogenation of these substrates *would be exceptionally challenging* due to the increase steric bulk around the olefin and the reduced propensity of Boc vs acetyl to associate with the metal catalyst; indeed, subjecting substrate **2v** to the standard conditions optimized for the *N*-acetyl protected substrates provided *no conversion* to product.[36] Moreover, attempts to prepare racemic product using Pd/C (120 psi H_2, 35 °C, MeOH) led only to competitive dechlorination of the chlorophenyl ring with the double bond untouched. Molecular modeling of *N*-Boc *β*-phenyl- and *β*,*β*-diphenylalanine methyl esters illustrate the steric congestion afforded by tetrasubstitution such that the phenyl groups are twisted out of conjugation and effectively shield both faces of the double bond (Figure 3).[37]

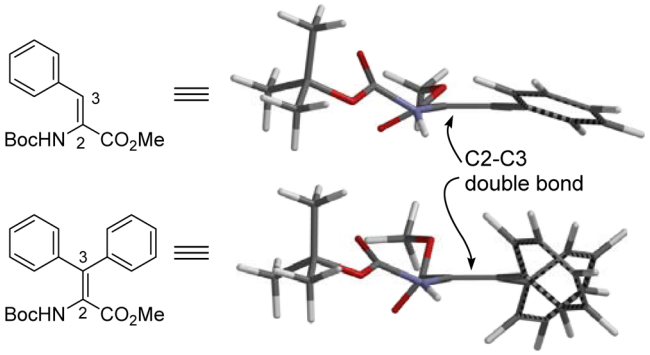


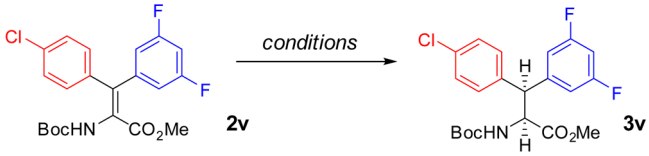
Figure 3. Ground state conformations of *N*-Boc *β*-phenylalanine and *β*,*β*-diphenylalanine methyl esters.

We returned to screening using $(NBD)_2RhBF_4$ as precatalyst and a variety of commercially available chiral phosphine ligands (Table 6, entries 1−3). Under these high catalyst loading conditions, previously identified ligand J011−1 gave high enantioselectivity but poor conversion (Table 6, entry 1). Ligand J013−1 and J212−1 gave good enantioselectivity and increased levels of reactivity (Table 6, entries 2−3). An examination of solvent effects with J212−1 showed a dramatic increase in reactivity as the solvent was changed from MeOH to EtOH to *i*PrOH (Table 6, entries 4−6); halogenated solvents DCE and PhCl also provided good results, but we selected *i*PrOH as the solvent of choice since it is more environmentally friendly.[38]

We were able to optimize the catalyst loading as low as 1 mol % by raising the reaction temperature from 50 to 80 °C. The higher temperature also allowed the reaction pressure to be lowered to a more practical 120 psi (Table 6, entries 9−13).

With revised conditions for *N*-Boc substrates defined, the substrate scope was evaluated. Gratifyingly, high enantioselectivities (92−99% ee) and conversion (>99%) were realized with good to excellent isolated yields (59−88%) obtained by direct crystallization for all the dehydroamino acid reductions examined (Table 5, entries 16−24). While we adopted 10 mol % of Rh and J212 ligand to evaluate the substrate scope, successful multigram scale reduction has been carried out at catalyst loadings as low as just 1.0 mol %. The ability to optionally access all possible

Table 6. Optimization of the Enantioselective Rh-Catalyzed Hydrogenation of Substrate 2v



entry	cond[a]	%Rh[b]	ligand[c]	solvent	conv[d]	%ee[d]
1	A	25	J011−1	MeOH	20	97
2	A	25	J013−1	MeOH	42	97
3	A	25	J212−1	MeOH	85	92
4	B	10	J212−2	MeOH	7	97[e]
5	B	10	J212−2	EtOH	67	98[e]
6	B	10	J212−2	*i*PrOH	91	97[e]
7	B	10	J212−2	DCE	97	96[e]
8	B	10	J212−2	PhCl	90	97[e]
9	C	10	J212−2	*i*PrOH	100	95[e]
10	C	5	J212−2	*i*PrOH	100	95[e]
11	C	2	J212−2	iPrOH	69	96[e]
12	D	2	J212−2	*i*PrOH	99	95[e]
13	D	1	J212−2	*i*PrOH	98	95[e]

[a]*Conditions*: $(NBD)_2RhBF_4$, MeOH. A: 0.016M, 500 psi H_2, 50 °C. B: 0.1M, 500 psi H_2, 50 °C. C: 0.5M, 500 psi H_2, 50 °C. D: 0.5M, 120 psi H_2, 80 °C. [b]Mol% Rh. A ratio of 1.05:1 Ligand/Rh was used. [c]See Figure 1 for ligand structures. J212−2 is the enantiopode of J212−1. [d]As determined by chiral HPLC at 210 nm. Absolute configuration (2*S*, 3*S*) unless otherwise stated. [e](2*R*, 3*R*).

stereoisomers for a given *β*,*β*-diaryl-*α*-amino acid is illustrated by the preparation of the 3,5-difluorophenyl-4-methoxyphenyl analogues (2*S*, 3*S*)-**3q**, (2*R*, 3*R*)-**3q** ≡ *ent*-**3q** and (2*S*, 3*R*)-**3z** (entries 22, 23 and 24). Preparation of the diastereomeric products (2*S*, 3*R*)-**3p** and (2*S*, 3*S*)-**3v** illustrate tolerance of a chlorine substituent with no evidence of competitive dechlorination under these more aggressive hydrogenation conditions (Table 5, entries 16 and 19). The absolute and relative stereochemistry was confirmed by the single crystal X-ray structure determination of **3v** (Figure 4).[39]

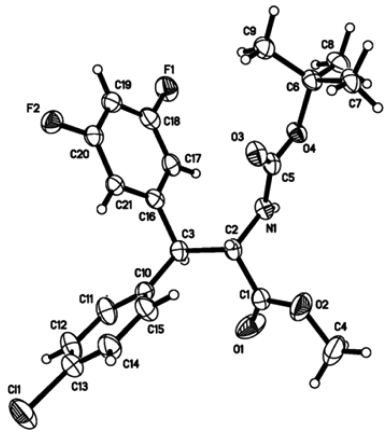


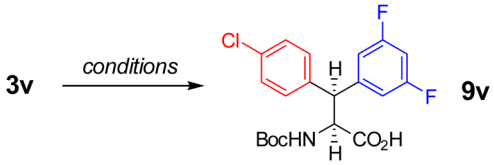
Figure 4. X-ray structure ORTEP plot of **3v** (thermal ellipsoids drawn at the 30% level).

The nonsymmetrically substituted *N*-protected *β*,*β*-diaryl-*α*-aminoesters reported in this paper are synthetically valuable chiral building blocks. In order to facilitate their subsequent coupling, we evaluated selectively hydrolyzing the esters revealing the corresponding acid. Initially, ester hydrolysis of **3v** to

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006

afford the corresponding *N*-Boc amino acid **9v** at first proved challenging with up 27% epimerization of the amino acid center when employing NaOH in aqueous THF (Scheme 4). DoE optimization of temperature, concentration, and equivalents using KOH in aqueous THF, followed by a further screen of polar solvents, identified aqueous *i*-PrOH at 50 °C as preferred. Application of these conditions to **3v** afforded **9v** as a crystalline solid in 79% yield with <1% epimer (Scheme 4).[40]

Scheme 4. Hydrolysis of *N*-Boc Amino Acid Ester 3v[a]



[a]*Conditions*: 3.0 equiv KOH, H_2O/*i*PrOH, 50 °C then HCl.

CONCLUSIONS

We have demonstrated the first synthesis of nonsymmetrically substituted *β*,*β*-diaryl *α*-amino acid esters through the asymmetric hydrogenation of highly congested tetrasubstituted olefins. The reaction conditions using $(NBD)_2RhBF_4$ and Josiphos ligands, allowed for outstanding control over the two vicinal stereogenic centers providing excellent enantioselectivities (88−99%) over a series of aryl and heteroaryl substituted substrates with Ac, methoxycarbonyl and less reactive Boc protected amines. Furthermore, preparation of either the *E*- or the *Z*- olefins was possible by the development of conditions to suppress scrambling during the enol tosylate Suzuki-Miyaura cross-coupling. This approach allowed for stereodivergent access to all four possible stereochemical isomers and is ideally placed to support drug discovery structure−activity relationship studies. Finally, a controlled hydrolysis of the methyl ester significantly enhances the practicality of the approach and the ability to leverage these valuable synthons in amino acid coupling chemistry.

ASSOCIATED CONTENT

Supporting Information

Characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

[§]The research described was partially carried out in 2010 at the former Merck Frosst Canada, Department of Process Research, Merck, 16711 Autoroute Transcanadienne, Kirkland, Québec, Canada, H9H 3L1.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dan Sorensen, Andrew Kirtley, Robert Reamer, Simon Hamilton, Andy Brunskill, and Tanja Brkovic for analytical support (Merck). The authors also acknowledge Scott Shultz, Jess Eastwood, Alejandro Dieguez-Vazquez, Stephen Keen, Michael Boyd, and Ernest Lee for technical assistance (Merck).

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(37) Geometry optimizations were performed using *Spartan'10*, version 1.1.0; Wavefunction, Inc.: Irvine, CA, 2011 using the B3LYP density functional with 6-31G* basis sets.
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(40) Hydrolysis of **3l** with 6N HCl in AcOH provides the corresponding amino acid hydrochloride salt.

DOI: 10.1021/ja511872a
J. Am. Chem. Soc. 2015, 137, 999−1006