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Enantioselective Conjugate Addition Nitro-Mannich Reactions: Solvent Controlled Synthesis of Acyclic *anti*- and *syn*-β-Nitroamines with Three Contiguous Stereocenters

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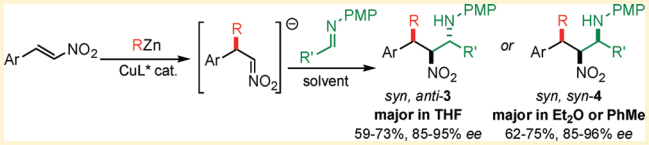
Supporting Information

ABSTRACT: We report an enantioselective conjugate addition nitro-Mannich reaction protocol which combines dialkylzinc, aromatic nitro alkene and imine to form two C−C bonds and three contiguous stereocenters in one reaction vessel. Absolute stereochemistry was controlled from the initial 1,4-addition of dialkylzinc to aromatic nitroalkenes by known copper−chiral ligand catalysts. The choice of solvent dictated the formation of either the *syn,anti* or *syn,syn* diastereoisomers, two of the four possible diastereoisomers. The *syn,syn* isomer is a rare example of a *syn*-selective nitro-Mannich reaction. The diastereoselectivity is dependent upon the presence or not of $Zn(O_2CCF_3)_2$ in the reaction mixture and empirical transition state models are proposed to account for the observed stereochemical course of the two reaction conditions. The extent of enantioselectivity and structural diversity of the process is limited by current methodology for the catalytic asymmetric addition of dialkylzincs to nitrostyrenes. The synthetically versatile products are the most complex β-nitro amines prepared using the nitro-Mannich reaction and are formed in high yield and enantioselectivity.



INTRODUCTION

The nitro-Mannich (or aza-Henry) reaction was characterized over 120 years ago,[1] but it is only since the development of stereoselective versions[2] that the broad versatility of the product β-nitroamines has been developed.[3] The *anti*-diastereoisomer dominates with higher homologues of nitromethane, with there being only two methods for a *syn*-selective nitro-Mannich reaction.[4] There are relatively few examples of the use of the nitro-Mannich reaction in total synthesis and its versatility has been limited by the availability of more complex nitroalkanes.[5] We envisaged that the conjugate addition of a nucleophile to a readily available nitroalkene (prepared via the Henry reaction) and subsequent trapping of the nitronate anion with an imine (Scheme 1) would not only give more diverse nitro coupling partners, but a convergent synthesis of acyclic β-nitro amines with three contiguous stereocenters. A related enantioselective one-pot reaction sequence has been reported by Dixon et al. for malonate-type nucleophiles and formaldehyde or cyclic imines. Diastereochemical control is very high and is due to the formation of the thermodynamically most stable cyclic product.[6] There are very few analogous acyclic sequences that have been described for the aldol,[7] Henry,[8] and Mannich[9] reactions, and these systems have been characterized for only one out of four possible diastereoisomers. We report here a synthetically flexible conjugate addition nitro Mannich reaction initiated by the asymmetric addition of dialkylzincs to a range of nitrostyrenes. In situ nitro-Mannich reaction with aryl or alkyl aldimines gives rise to a choice of either *anti*- or the rare *syn*-β-nitroamines, dependent upon solvent, with excellent enantiocontrol over three contiguous stereocenters (Scheme 2).

RESULTS AND DISCUSSION

Initial studies began with the Cu-catalyzed addition of diethylzinc to β-nitrostyrene as there are numerous reported asymmetric protocols for this particular addition[10] and the stereocenter generated should provide the best facial bias for subsequent addition to the intermediate nitroante anion (vide infra). Copper-catalyzed addition of Et_2Zn to β-nitrostyrene **1** in THF was complete in 1 h (Scheme 2). Cooling **2** to −78 °C and addition of PMP-protected imine **3** and TFA at −78 °C for 1 h and then warming to rt for 1 h provided β-nitroamines **4a**−**c** in high conversion (80%) with a modest diastereomeric ratio of 75:20:5 (Table 1, entry 1). The corresponding OMB-protected imine led to a similar conversion, but no dr. This is reminiscent of its nullifying effect in catalytic asymmetric nitro-Mannich reactions.[11] Conducting the reaction in Et_2O under identical reaction conditions gave a >95% conversion to β-nitroamines **4a**−**c** with a diastereomeric ratio of 10:85:5 (entry 4). The stereochemical assignment of diastereoisomers *syn,anti*-**4a** and

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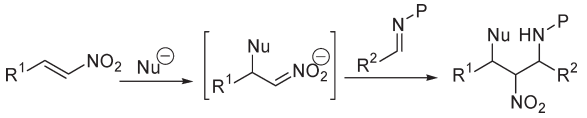
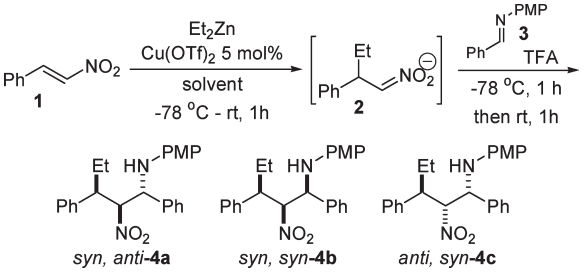
Scheme 1. Conjugate Addition Nitro-Mannich Reaction



Scheme 2. Observed Products of Conjugate Addition Nitro-Mannich Reaction



syn,syn-**4b** were confirmed by single-crystal X-ray crystallography (see the Supporting Information). The relative stereochemistry of *anti,syn*-**4c** is tentatively assigned on the basis of our previous observation that the *syn*-β-nitroamines are normally more configurationally stable than their *anti*-isomers.[2a,2e] The *anti,anti*-diastereoisomer of **4** was not detected. A solvent screen showed a pronounced effect on diastereoselectivity (Table 1). Strongly Lewis basic solvents (entries 1−3) were found to promote the formation of the *syn,anti*-product **4a**, whereas less Lewis basic solvents promoted the formation of the *syn,syn*-diastereisomer **4b** (entries 4−8); *syn*-selectivity for the nitro-Mannich reaction is unusual.[4] All of the reaction mixtures that formed *syn,syn*-**4b** as the major product were heterogeneous (entries 4−8). The colorless precipitate was isolated and revealed to be zinc trifluoroacetate by ^{19}F NMR comparison with an authentic sample. It would seem that its dissolution or not in the reaction mixture has a dramatic effect on the observed diastereoselectivity of the product (compare entries 1 and 4, Table 1). From this solvent screen, THF and Et_2O were selected to investigate complementary enantioselective conjugate addition nitro-Mannich reactions to control the absolute stereochemistry for two of the four possible diastereoisomers in this one-pot sequence of reactions.

Under the same reaction stoichiometry (Table 1, footnote a), an investigation of reaction time versus temperature after the addition of the imine and TFA at −78 °C revealed that in THF, the time from removal of the cooling bath to quench was crucial (Table 2, entries 1−4) with 5 min proving optimal. The internal temperature of the reaction at this point was around −40 °C. Longer reaction times at rt led to an erosion of the *syn,anti*-**4a** diastereoisomer to *syn,syn*-**4b** to a level of ∼1:1 and eventually to some retro-addition/decomposition (24 h). Longer periods at −78 °C had no effect (entry 5). Warming the reaction directly to rt from −78 °C led to poor stereoselectivity (entry 6), very similar to reactions allowed to stir for 1 h or more at rt (entry 3). This suggested the reaction was occurring during the warming period. Warming the reaction directly to −42 °C from −78 °C and quenching the reaction after 5 min gave *syn,anti*-**4a** (75:15:10, entry 7) which would support this. Leaving the reaction at −42 °C for longer periods resulted in erosion of the dr in favor of *syn, syn*-**4b**. Leading on from these studies, in Et_2O the reaction gave slightly better *syn, syn*-diastereoselectivity and conversion if it was allowed to equilibrate to rt and stir over 1 h (entries 8−10). Internal temperature monitoring revealed rt was reached after ∼15 min. Longer reaction times at −78 °C or rt led to no improvement of the reaction (entries 11 and 12).

These results led us to conclude that *syn,anti*-**4a** is the kinetic product of the reaction in THF. Its epimerization to the *syn*-nitro-Mannich product **4b** (or **4c**) over longer periods of stirring at rt could be due to epimerization of the acidic C*H*NO_2 stereocenter or, we think more likely, due to retro-addition and recombination to give a thermodynamically more stable *syn*-β-niroamine. The *syn*-β-nitroamine can adopt an H-bonded chair conformation with all substituents equatorial.[2a] In Et_2O there is a small increase in diastereoselectivity upon allowing the reaction to reach ambient temperature after 30 min or more, and prolonged stirring at rt does not seem to alter the diastereoselectivity to a significant extent. We speculate that under these reaction conditions the most stable product is formed and that it is also the kinetic product as we see far higher levels of

Table 1. Effect of Solvent on Diastereoselection[a]

entry	solvent[b]	conversion to **2** (%)[c]	conversion to **4** (%)[c]	dr **4a**:**4b**:**4c**[d]
1	THF	>95	80	75:20:5
2	DME	80	80	45:10:45
3	Me_2CO	∼50	∼50	50:5:45
4	Et_2O	>95	>95	10:85:5
5	TBME	>95	80	20:75:5
6	$^iPr_2O$	>95	70	10:85:5
7	CH_2Cl_2	>95	85	10:80:10
8	PhMe	85	80	25:70:5

[a] Reactions carried out with 5 mol % of $Cu(OTf)_2$, 1.1 equiv of $ZnEt_2$, 2 equiv of imine, 3.5 equiv of TFA, stirred at −78 °C for 1 h, then at rt for a further 1 h. [b] 1,4-Dioxane, DMF, and EtCN gave no 4. [c] Determined by ^{1}H NMR. [d] Determined by comparison of the ^{1}H NMR signals for $CHNO_2$ (∼5 ppm) or the CHEt signals (∼3.5 ppm).

Table 2. Investigation of Reaction Temperature and Time

entry	solvent	time at −78 °C[a] (h)	time[b]	conversion to **4** (%)[c]	dr **4a**:**4b**:**4c**[d]
1	THF	1	0	<10	∼45:45:10
2	THF	1	5 min	>95	85:10:5
3	THF	1	1 h	>95	60:20:20
4	THF	1	16 h	90	45:45:10
5	THF	4	5 min	90	85:10:5
6	THF	1	5 min[e]	>95	50:40:10
7	THF	1	5 min[f]	>95	75:15:10
8	Et_2O	1	5 min	85	20:75:5
9	Et_2O	1	30 min	90	10:85:5
10	Et_2O	1	1 h	>95	10:85:5
11	Et_2O	4	1 h	>95	10:80:10
12	Et_2O	2	16 h	>95	10:80:10

[a] Time after addition of imine and TFA. [b] Time from when removed from cooling bath and allowed to warm. [c] *Determined by ^{1}H NMR.* [d] Determined by comparison of the ^{1}H NMR signals for C*H*NO_2 (∼5 ppm) or the C*H*Et signals (∼3.5 ppm). [e] Reaction vessel placed in a water bath at rt directly from −78 °C. [f] Reaction vessel placed in a MeCN/dry ice bath at −42 °C directly from −78 °C.

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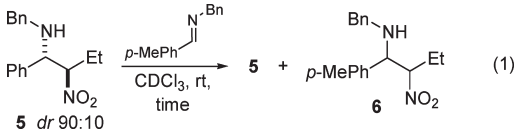
Table 3. Erosion of Diastereoselectivity by Retro-addition/Re-addition

		control	mixture	
entry	time/h	**5** *anti/syn*	**5** % (*anti/syn*)	**6** % (*anti/syn*)
1	0	90:10	100 (90:10)	0
2	6	90:10	95 (85:15)	5 (>95:5)
3	20	80:20	75 (75:25)	25 (65:35)
4	30	75:25	70 (65:35)	30 (60:40)
5	48	65:35	60 (55:45)	40 (50:50)
6	72	55:45	55 (40:60)	45 (45:55)
7	144	35:65	50 (25:75)	50 (35:65)

syn-diastereoselectivity than we have ever seen under any equilibrating reaction conditions[2e] and no products from retro-addition/decomposition. The instability of *syn,anti*-**4a** pre-empted any equilibration studies in Et_2O. However, a cross-over experiment using a more stable nitro-Mannich product **5** lends support to our hypothesis (eq 1, Table 3). Treatment of pure **5** (original dr *anti/syn* 90:10) with a stoichiometric amount of the imine derived from *p*-tolylaldehyde in $CDCl_3$ at rt gradually led to an erosion and eventual reversal of dr for the original nitro-Mannich product (**5**) and the equal formation of the *p*-tolyl nitro-Mannich product **6** with *syn* enrichment. A control NMR tube contained just β-nitroamine **5** for comparison purposes. The ~1:3 *anti/syn* diastereoselectivity that both **5** and **6** settled down to was typical of selectivities observed with thermodynamic preparations of nitro Mannich products we have conducted.[2e]



(1)

A selection of nitroalkenes and imines were surveyed for enantio- and diastereocontrol under the two reaction conditions (Table 4). Diastereoselectivities are quoted from analysis of the crude reaction mixture and after purification and are uniformly very high. This was due to the judicious choice of the newly created stereocenter, derived from the conjugate addition reaction, possessing substituents (aryl-^{n}alkyl-H) that maximized the possibility for stereofacial bias. Conjugate addition of diethylzinc to ^{i}PrCH=CHNO$_2$ followed by nitro-Mannich reaction (Et_2O) gave the desired product in 74% isolated yield, but a dr of only 5:3 (*syn,syn/anti,syn*). Clearly, the substituents ^{s}alkyl-^{n}alkyl-H do not provide a sufficient stereofacial bias based on sterics.

The relative instability of β-nitroamines is due, in part, to the accessibility of the amine lone pair of electrons. It has been shown that *N*-Boc and *N*-phosphonoyl β-nitroamines are amenable to chromatography, whereas *N*-PMP, *N*-OMB, *N*-Bn and *N*-alkyl β-nitroamines are less stable.[2] We therefore attempted to delocalize the lone pair of the β-nitroamine products by the introduction of an electron-withdrawing protecting group. Attempts using standard conditions for PhCOCl, $(Boc)_2O$, TsCl, MeI with Et_3N, and/or DMAP in CH_2Cl_2 had all failed. It was found that treatment of β-nitroamines with $(TFA)_2O$ in the presence of Hünig's base provided β-nitroacetamides in high yield from nitroalkenes.[12] The protection was complete almost immediately at 0 °C, and the product β-nitroacetamides were found to be

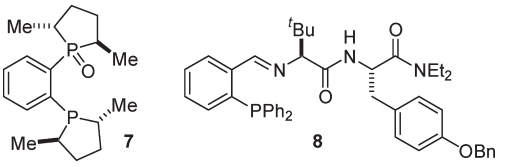
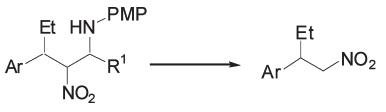


Figure 1. Ligands for asymmetric process.

stable to chromatography, strong acid, heat, and prolonged periods in solution (>1 month). To aid purification, the *syn, anti*-**a** diastereoisomers from the THF experiments (entries 1−14) were isolated as their *N*-trifluoroacetamides. The minor *syn,syn*-**b** diastereoisomers contained in these reactions were inert to this protection step and thus the purified products from the THF reactions were enriched in the *syn, anti*-**a** diastereoisomers with minor amounts of the *N*-trifluoroacetamide protected *anti,syn*-**c** diastereoisomer. The *syn,syn*-**b** diastereoisomer-rich reactions (entries 15−25), which were inert to trifluoroacetamide formation, were sufficiently stable to be purified by a rapid silica gel column. The *syn,anti*-**a** and the *anti,syn*-**c** diastereiosmers decomposed during this purification, and the purified material was isolated solely as the *syn,syn*-**b** diastereoisomers. The control of absolute stereochemistry came from the initial copper-catalyzed 1,4-addition, and we surveyed a number of known asymmetric ligands which revealed two that were compatible with our particular diastereoselective reaction conditions. The Charette procedure[10a] using BozPHOS (**7**, Figure 1) with Et_2O as solvent provided isomer **b**. A solvent swap after the 1,4-addition from Et_2O to THF ensured efficient preparation of isomer **a**. The Hoveyda protocol[10b] with ligand system **8** (Figure 1) used PhMe as solvent and under optimized conditions were found to be comparable to using Et_2O to give isomer **b**. Again, a solvent swap after the 1,4-addition from PhMe to THF ensured efficient preparation of isomer **a**.

Enantioselectivites were measured by HPLC using a chiral stationary phase with retention times compared to racemic standards. If the products could not be separated by a chiral stationary phase, they were measured by degradation (eq 2). For the *syn,anti* isomers **a**, as is normal for the types of *anti*-β-nitroamines we generate, the NMR solutions gradually underwent retro addition if left in $CDCl_3$ at rt.[2a] Samples were left until complete degradation (1−2 days) by ^{1}H NMR and the crude nitroalkane was then used for HPLC analysis to measure the enantiomeric excess of the parent β-nitroamine. For the *syn,syn* isomers **b**, a small sample (ca. 20 mg) was dissolved in THF (3 mL) with a small amount of TFA (0.2 mL) added. The yellow solution was heated at reflux for 5 h before being cooled to rt. The crude nitroalkane was isolated by aqueous workup and then used for HPLC analysis to measure the enantiomeric excess of the parent β-nitroamine. These processes were validated by subjecting entry 18, Table 4 (Ar = Ph, R = Et, R^1 = *p*-Me-Ph) measured by chiral HPLC (OD-H column, 99.5% hexane 0.5% IPA) to be 96% ee to the above conditions, which showed the parent nitroalkane had 95% ee.



(2)

The *syn,anti* isomers **a** were obtained in high conversion and stereoselectivity (Table 4). Representative aryl/heteroaryl

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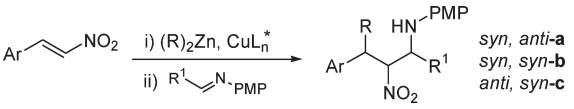
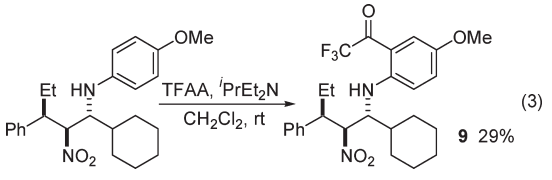
Table 4. Scope of Reaction



entry	Ar	R	R^1	solvent	ligand	dr **a**/**b**/**c**[a] crude	dr **a**/**b**/**c**[a] purified	yield (%)	ee[b] (%)
1[c]	Ph	Et	Ph	THF	**7**	85:10:5	90:0:10	73	86[d]
2[c]	Ph	Et	*p*-Cl-Ph	THF	**7**	55:15:30	80:0:20	59	85[e]
3[c]	Ph	Et	*p*-Me-Ph	THF	**7**	75:15:10	95:0:5	61	85[e]
4[c]	Ph	Et	*n*-Pn	THF	**7**	95:5:0	100:0:0	68	90[e]
5[f]	Ph	Et	2-furyl	THF	**8**	90:10:0	100:0:0	69	92[d]
6[f]	Ph	Et	2-thienyl	THF	**8**	95:5:0	100:0:0	74	95
7[f]	*p*-Me-Ph	Et	Ph	THF	**8**	70:15:15	85:0:15	70	90[d,e]
8[g]	Ph	Me	Ph	THF	**8**	85:10:5	100:0:0	62	98
9[f]	2-furyl	Et	Ph	THF	**8**	90:10:0	100:0:0	74	89[d]
10[f]	2-thienyl	Et	Ph	THF	**8**	80:10:10	90:0:10	80	90[d,e]
11[f]	*p*-MeO-Ph	Et	Ph	THF	**8**	90:10:0	100:0:0	73	90
12	*p*-O_2N-Ph	Et	Ph	THF	-	75:10:15	90:0:10	38	-
13	*o*-F_3C-Ph	Et	Ph	THF	-	5:10:0:85[h]	5:0:0:95[d,h]	38	-
14	*o*-MeO-Ph	Et	Ph	THF	-	50:50:0	50:50:0	4	-
15[i]	Ph	Et	Ph	Et_2O	**7**	5:95:0	0:100:0	62	90[d,e]
16[j,k]	Ph	Me	Ph	PhMe	**8**	5:95:0	0:100:0	72	93
17[i]	Ph	Et	*p*-Cl-Ph	Et_2O	**7**	5:95:0	0:100:0	74	90[e]
18[i]	Ph	Et	*p*-Me-Ph	Et_2O	**7**	5:95:0	0:100:0	70	96[d]
19[i]	Ph	Et	2-furyl	Et_2O	**7**	5:95:0	0:100:0	72	92
20[j]	Ph	Et	2-thienyl	PhMe	**8**	5:95:0	0:100:0	75	95
21[j]	*p*-Me-Ph	Et	Ph	PhMe	**8**	5:95:0	0:100:0	69	88
22[j]	2-furyl	Et	Ph	PhMe	**8**	5:95:0	0:100:0	71	85[d]
23[j]	2-thienyl	Et	Ph	PhMe	**8**	5:95:0	0:100:0	77	86
24[j]	*p*-MeO-Ph	Et	Ph	PhMe	**8**	5:95:0	0:100:0	75	88[d]
25[l]	*p*-O_2N-Ph	Et	Ph	PhMe	-	10:90:0	0:100:0	54	-
26[j]	Ph	Et	CO_2Et	PhMe	**8**	95:5:0	100:0:0	69	95[d,e]

[a] Determined by comparison of the ^{1}H NMR signals for $CHNO_2$ (~5 ppm) or the CHEt signals (~3.5 ppm). [b] Measured by chiral HPLC (OD-H column, 99.5% hexane 0.5% IPA). [c] Cu(**7**)$_2$OTf (5 mol %), pivalamide (80 mol %), Et_2Zn, −70 °C, Et_2O, 20 h. Solvent removed under reduced pressure and THF added before nitro Mannich reaction. Product isolated as trifluoroacetamide (TFAA, DIPEA, CH_2Cl_2, rt) to give 1*R*, 2*S*, 3*R*-*syn, anti*-a. [d] Structure determined by X-ray; see the Supporting Information. [e] Measured by chiral HPLC of parent nitroalkane (OD-H column, 98% hexane, 2% IPA); see the Supporting Information. [f] $(CuOTf)_2\cdot$PhMe (1 mol %), ligand **8** (2 mol %), PhMe, −40 °C to rt, 16 h, then same as b to give 1*S*, 2*R*, 3*S*-*syn, anti*-a. [g] Procedure f using Me_2Zn. [h] *anti, anti*-Diastereoisomer. [i] Cu(**7**)$_2$OTf (5 mol %), pivalamide (80 mol %), Et_2Zn, −70 °C, Et_2O, 20 h to give 1*S*, 2*S*, 3*R*-*syn*, *syn*-b. [j] $(CuOTf)_2\cdot$PhMe (1 mol %), ligand **8** (2 mol %), PhMe, −40 °C to rt, 16 h to give 1*R*, 2*R*, 3*S*-*syn*, *syn*-b. [k] Procedure from footnote j using Me_2Zn. [l] 1,4-addition in THF, solvent swapped to PhMe before addition of imine.

nitroalkenes showed the reaction gave uniformly high yields and enantioselectivities (entries 1−11, 85−98% ee). The aldimine partner can be derived from aryl, heteroaryl, alkyl, and ester substituents (entry 26). Use of the imine derived from cyclohexyl aldehyde under the *syn,anti-* protocol gave crude selectivity (80:10:10) in good conversion, but standard TFA protection led to the isolation of a Fries-type product **9** (eq 3) in 29% yield among degradation products. There are two more obvious possible mechanisms for this reaction, either a Friedel−Crafts acylation or a Fries rearrangement. Although Friedel−Crafts acylations using protic acids are known, the conditions required are very harsh, usually requiring refluxing and a superstoichiometric amount of a strong acid. This leads us to believe that formation was first through acylation on nitrogen, then subsequent rearrangement. This is, in itself, quite a rare reaction. The large majority of aniline based Fries rearrangements are photochemical reactions,[13] and only a limited amount of literature is available on this type of thermal process.[14]



(3)

The corresponding conjugate addition nitro Mannich reactions in Et_2O or PhMe led to similar results for *syn,syn*-**b** (entries 14−24) in uniformally high yields and enantioselectivities (84−96%) for a range of aryl/heteroaryl nitroalkenes and aryl/heteroaryl imines. Certain substituents on the aromatic ring of nitrostyrenes did not give enantioselectivities (entries 12−14 and 25). The solubility of *p*-NO_2-*β*-nitrostyrene is minimal in

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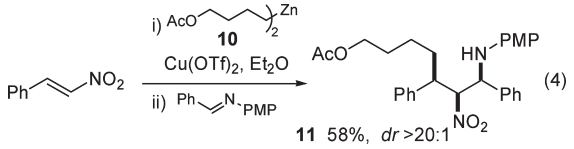
Et_2O or PhMe. Even after prolonged stirring in Et_2O or PhMe < 20% reaction was observed using the Hoveyda protocol and no conversion with the Charette protocol was observed. Performing the entire reaction sequence in THF led to racemic *syn,anti*-selectivity but in only 39% yield (entry 12). By using THF as the solvent for the 1,4-addition, then replacing with PhMe for the nitro-Mannich step, racemic *syn,syn*-product was isolated in good yield (54%, entry 25). Unfortunately, *p*-CF_3 β-nitrostyrene gave no nitro-Mannich reaction in either solvent. However, *o*-CF_3 β-nitrostyrene led to the isolation of the previously unseen *anti, anti*-diastereoisomer in low yield (38%, entry 13). An electron-donating *o*-MeO substituent in β-nitrostyrene led to a poor (5%) conversion in THF with loss of diastereoselectivity in the nitro-Mannich step (entry 14) and no conversion in Et_2O. An *o*-Me substituent in β-nitrostyrene led to no reaction in THF or Et_2O. Under the reaction conditions for the production of *syn,syn*-diastereoisomer **b**, the glyoxylate imine (entry 26) gave the *syn, anti*-diastereoisomer **a** instead of the expected *syn,syn*-**b**. Inspection of the reaction mixtures revealed it was homogeneous like the THF experiments. The *n*-pentyl imine (entry 4) also gave *syn, anti*-diastereoselectivity when run in either Et_2O or PhMe and these reactions were also homogeneous. It would seem that the precipitation of $Zn(O_2CCF_3)_2$ is crucial for the formation of the *syn* nitro-Mannich isomer. Addition of pentane to force precipitation in these two experiments led to the imine separating from the solution and resulted in no reaction.

To investigate alternative alkylzinc reagents, dimethylzinc (entries 8 and 16) provided the desired β-nitroamines in good yield and excellent ee. The enantioinduction observed was in line with those observed by Charette and Hoveyda.[10] We also investigated the addition of diphenylzinc to 1-nitrobut-1-ene, but unfortunately, diphenylzinc did not give any enantioinduction with the Hoveyda ligand (THF, 64%, dr 90:0:10; PhMe, 63% 0:100:0) and no conversion with the Charette ligand. There is no literature precedent for the use of diphenylzinc in the asymmetric addition to a nitroalkene. Functionalized diorganozinc reagents also participate in the conjugate addition nitro-Mannich reaction sequence (eq 4). Using the tandem hydroboration/boron−zinc exchange method developed by Knochel,[15] the functionalized diorganozinc reagent **10** reacted under the Et_2O protocol to give *syn,syn*-**11** in 58% yield, essentially as a single diastereoisomer. Attempting to induce absolute stereochemistry by using the Charette or Hoveyda protocols gave racemic material. These results are indicative of the limitations in the asymmetric addition of functionalized diorganozinc reagents to β-nitrostyrenes. The enantioselectivity of the conjugate addition nitro-Mannich reaction is bounded by the efficiency of chirality transfer in the initial conjugate addition reaction.



11 58%, *dr* >20:1

The difference in the sense of diastereoselectivity for each reaction protocol can be understood by an analysis of each stereodetermining element. As the relationship between the alkyl stereocenter derived from the conjugate addition and the nitro stereocenter from the nitro-Mannich reaction is *syn* for both reaction protocols we may assume a similar reactive conformation of the nitronate is operating in each. The control of the

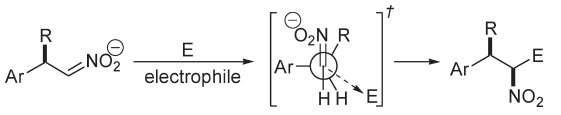


Figure 2. Houk-type analysis of electrophilic attack adjacent to an α-stereocenter dictated by sterics.

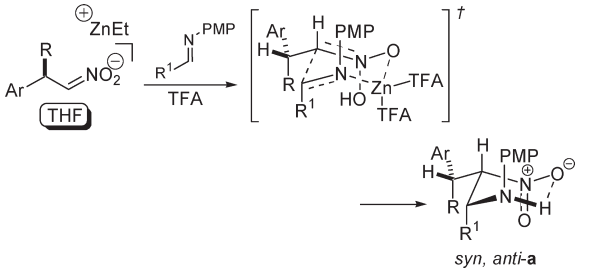


Figure 3. Closed transition-state analysis to account for homogeneous reactions.

diastereoselectivity from the initial conjugate addition step will be dictated by the energetics of electrophilic addition adjacent to an α-stereocenter. Houk has calculated that the trajectory of an electrophilic addition adjacent to an α-stereocenter, ignoring any stereoelectronic effects that normally arise from polar substituents on the directing center, is energetically most favorable from a Felkin−Anh like reactive conformation (Figure 2).[16] This analysis correctly predicts the major *syn*-diastereoselectivity observed in both addition protocols between the alkyl stereocenter derived from the conjugate addition and the nitro stereocenter from the nitro-Mannich reaction. We think it is reasonable to assume there will be little stereoelectronic bias from the directing stereocenter as it is devoid of polar substituents.

The diastereoselectivity between the nitro-Mannich stereocenters in the two solvent-dependent reaction protocols suggests that two distinct reaction trajectories are operating. If for the homogeneous reactions in THF we assume a closed Zimmerman−Traxler-like cyclic transition state between the nitronate and imine,[17] which has been our working hypothesis to account for the usual formation of the *anti*-β-nitroamine stereochemistry,[2a,2e] and that the imine stereochemistry is preserved upon coordination of the Zn^{2+} species, then a classic chair like transition state can most simply account for the major *syn, anti*-diastereoselectivity (Figure 3). The chiral nitronate side chain occupies an equatorial orientation with the facial selectivity dictated as discussed above.

This explains not only the observed *anti*-relationship between the nitro-Mannich stereocenters but also why the reaction time has such an effect on the diastereoselectivity. The diastereoselectivity for the reaction in THF is at its peak 5 min after removing the vessel from the cold bath (entry 2, Table 2). If the reaction is left for longer at rt the diastereoselectivity drops until after 16 h the *syn/anti*:*syn/syn* ratio is 1:1 (entry 4, Table 2). We believe the reaction is under kinetic control at low temperatures, but at higher temperatures becomes reversible and may operate under thermodynamic control. Thus, over time the amount of the thermodynamically more stable *syn*-nitro-Mannich product increases (*syn*-nitroamines in a hydrogen bonded chair can align all substituents in an equatorial position).[2e]

In less polar solvents, precipitation of the Zn^{2+} could encourage an open transition state to be operative. If eclipsed open

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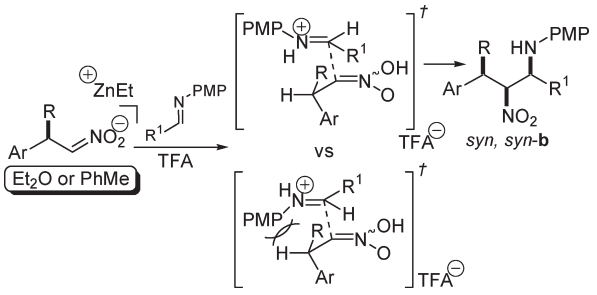

Figure 4. Open transition-state analysis to explain *syn, syn*-**b** diastereoselectivity.

transition states are discounted on steric grounds and the trajectory of the energetically more favored staggered conformations of the imine to the least hindered face of the nitronate are considered to be dictated by the minimization of dipole−dipole interactions,[18] then the diastereocontrol of the nitro-Mannich stereocenters can be understood by avoiding the unfavorable steric interaction between the chiral nitronate substituent and the *N*-PMP group (Figure 4). This analysis taken together with the facial bias of the nitronate species (Figure 2) correctly accounts for the formation of the major *syn,syn*-**b** diastereoisomer in the heterogeneous reactions using Et_2O or PhMe.

■ CONCLUSION

In summary, we have developed the first catalytic asymmetric protocol for the acyclic 1,4-addition nitro-Mannich reaction demonstrated with a carbon nucleophile. Asymmetric 1,4-addition of dimethyl or diethyl zinc to aryl/heteroaryl nitroalkenes provides the necessary facial bias around the nitronate ion to control, in conjunction with the choice of solvent, the formation of *syn,anti*-**a** or the more unusual *syn,syn*-**b** products in high yield and enantioselectivity. There are many ways of generating more complex dialkylzincs that will be applicable in this process, but the control of absolute stereochemistry is currently bounded by the limitations of current methodology for the asymmetric conjugate addition of alkyl nucleophiles to nitrostyrenes. These and the asymmetric 1,4-addition of hydride and heteroatom nucleophiles in the conjugate addition nitro-Mannich reaction are under investigation.

■ EXPERIMENTAL SECTION

General Procedure for the Synthesis of *syn,anti*-β-Nitroamines (Table 4) (a). *Using Cu(**7**)$_2$OTf and THF.* To a stirred mixture of nitroalkene (1.00 mmol), Cu(**7**)$_2$OTf (0.05 mmol), and pivalamide (0.80 mmol) in Et_2O (5 mL) at −70 °C was added R_2Zn (1.1 mmol, 1 M in hexanes) dropwise. The mixture was stirred at this temperature until the reaction was complete by TLC analysis (approximately 20 h). The solvent was removed using Schlenk techniques, replaced with THF (8 mL), and cooled to −78 °C. A solution of imine (2 mmol) in THF (1 mL) was added and stirred for 5 min. A solution of TFA (3.5 mmol) in THF (1 mL) was then added dropwise, and the reaction was stirred at −78 °C for 1 h, removed from the cold bath and stirred for 5 min, and then quenched with saturated aq $NaHCO_3$ (15 mL). The layers were separated, the aqueous phase was extracted with Et_2O, the combined organics were washed with satd $NaHCO_3$ and brine and dried ($MgSO_4$), and solvent was removed in vacuo to provide crude β-nitroamine. Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the C*H*CHNO$_2$ protons (~3.1−3.6 ppm). The crude β-nitroamine was immediately dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C, and DIPEA (2.2 mmol) and $(TFA)_2O$ (2.2 mmol) were added. The reaction was warmed to rt and stirred for 1 h before the addition of 2 M HCl (10 mL). The organic layer was washed with 2 M HCl and dried ($MgSO_4$) and solvent removed. The crude β-nitroacetemide was then purified by column chromatography to yield diastereomerically pure (1*R*,2*S*,3*R*)-*syn,anti*-β-nitroacetamides (Table 4, entries 1−4).

*Using Ligand **8** and THF.* Ligand **8** (0.02 mmol) and $(CuOTf)_2\cdot$PhMe (0.01 mmol) were added to a flame-dried flask in a glovebox, and the flask was equipped with a septum. The flask was removed from the glovebox and dry PhMe (2 mL) added. The suspension was stirred at rt for 10 min to provide a yellow solution. The solution was cooled to −30 °C and stirred for 10 min before R_2Zn (1.1 mmol, 1 M in hexanes) was added dropwise and stirred for 10 min to provide an orange solution. A solution of nitroalkene (1 mmol) in PhMe (2 mL) was added over 5 min and stirred for 20 min before being warmed to rt to provide a yellow solution. The reaction was stirred at rt until complete by TLC analysis (approximately 16 h). The reaction then proceeded as above to yield diastereomerically pure pure (1*S*,2*R*,3*S*)-*syn,anti*-β-nitroacetamides (Table 4, entries 5−11).

Data for *syn,anti*-a (Table 4). *Entry 1: Cu(**7**)$_2$OTf, THF.* Isolated as a 90:0:10 mixture of diastereoisomers as a white solid (231 mg, 71%): mp 128.5−130.8 °C; R_f 0.21 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ −24.1 (*c* 0.41, $CHCl_3$); IR ν_{max} 2971, 2841, 1698, 1607, 1555, 1511, 1182 cm^{-1}; ^{1}H NMR δ 0.83 (3H, t, *J* = 7.3), 1.77 (1H, ddq, *J* = 11.9, 11.8, 7.2), 2.16 (1H, dqd, *J* = 13.7, 7.3, 3.0), 3.21 (1H, ddd, *J* = 11.8, 4.8, 3.0), 3.81, (3H, s), 5.66 (1H, dd, *J* = 10.5, 4.9), 6.18 (2H, d, *J* = 10.1), 6.56 (1H, dd, *J* = 8.8, 2.8), 6.83 (2H, m), 7.15−7.25 (4H, m), 2.28−7.43 (4H, m); rotameric peaks 0.92 (3H, t, *J* = 7.4), 3.35 (1H, m), 3.84 (3H, s), 6.61 (1H, m); ^{13}C NMR δ 12.2 (CH_3), 23.1 (CH_2), 48.0 (*C*H), 55.4 (CH_3), 63.5 (*C*H), 91.6 (*C*H), 116.3 (q, *J* = 288.8, *C*F$_3$), 127.7 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 129.0 (*C*H), 129.3 (*C*H), 129.4 (*C*H), 129.7 (*C*H), 130.5 (*C*H), 132.2 (*C*H), 133.2 (*C*H), 133.3 (*C*), 134.8 (*C*), 136.6 (*C*), 139.0 (*C*H), 158. Two (q, *J* = 35.8, *C*=O), 160.4 (*C*H); rotameric peaks 12.5 (CH_3), 26.4 (CH_2), 48.2 (*C*H), 90.7 (*C*H), 116.4 (q, *J* = 288.8, *C*F$_3$), 158.3 (q, *J* = 35.8, *C*=O), 160.4 (*C*); ^{19}F NMR ($CDCL_3$, 376 MHz) δ −67.0 (3F, s, *C*F$_3$); *m*/*z* (ESI$^+$) 509 (100, M + Na$^+$), 504 (14, M + NH_4^+); HRMS $C_{26}H_{25}F_3N_2NaO_4$ calcd 509.1659, found 509.1653, $C_{26}H_{29}F_3N_3O_4$ calcd 504.2105, found 504.2102; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}), 17.5 min (minor), 19.8 (major), shows 85% ee. Anal. Calcd. For $C_{26}H_{25}F_3N_2O_4$: C, 64.19; H, 5.18; N, 5.76. Found: C, 64.17; H, 5.22; N, 5.63. X-ray structure confirmed relative stereochemistry (Supporting Information).

*Entry 2: Cu(**7**)$_2$OTf, THF.* Isolated as a 80:0:20 mixture of diastereoisomers as a yellow oil (206 mg, 59%): R_f 0.29 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ −2.5 (*c* 0.83, $CHCl_3$); IR ν_{max} 3011, 2967, 2878, 1698, 1606, 1555, 1511, 1256, 1182 cm^{-1}; ^{1}H NMR δ 0.78 (3H, t, *J* = 7.3), 1.75 (1H, m), 2.07 (1H, m), 3.15 (1H, ddd, *J* = 14.7, 5.3, 3.0), 3.78 (3H, s), 5.66 (1H, dd, *J* = 10.2, 5.4), 6.06 (1H, d, *J* = 10.1), 6.22 (1H, d, *J* = 7.9), 6.61 (1H, dd, *J* = 8.8, 2.7), 6.79−6.90 (3H, m), 7.17 (4H, m), 7.37 (3H, m); rotameric peaks 0.53 (3H, t, *J* = 7.3), 2.06 (1H, m), 3.30 (1H, m), 3.81 (3H, s), 6.02 (1H, d, *J* = 9.1), 6.66 (1H, m); ^{13}C NMR δ 12.0 (CH_3), 23.3 (CH_2), 48.1 (*C*H),55.5 (CH_3), 62.9 (*C*H) 91.4 (*C*H), 113.8 (*C*H), 114.0 (*C*H), 116.1 (q, *J* = 290.4, *C*F$_3$), 127.1 (*C*), 127.5 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 130.1 (*C*H), 130.5 (*C*H), 131.3 (*C*H), 131.5 (*C*), 135.6 (*C*), 138.6 (*C*), 158.4 (q, *J* = 36.0, *C*=O), 160.4 (*C*); rotameric peaks 26.3 (CH_2), 90.6 (*C*H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −67.1 (3F, s, CF_3); *m*/*z* (ESI$^+$) 543 (M + Na$^+$, 100), 538 (M + NH_4^+, 61); HRMS $C_{26}H_{24}ClF_3N_2NaO_4$ calcd 543.1269, found 543.1263, $C_{26}H_{28}ClF_3N_3O_4$ calcd 538.1715, found 538.1699; HPLC measured for parent nitroalkane obtained via retro-addition (Chiracel OD-H 150 mm column with guard, 98:2 hexane/EtOH, 0.5 mL min^{-1}) 11.5 min (major), 14.3 min (minor) shows 85% ee.

*Entry 3: Cu(**7**)$_2$OTf, THF.* Isolated as a 95:0:5 mixture of diastereoisomers as a yellow semisolid (203 mg, 61%): R_f 0.36 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ −15.0 (*c* 0.51, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3010, 2969, 2842, 1697, 1605, 1555, 1511, 1182 cm^{-1}; ^{1}H δ 0.81 (3H, t, *J* = 7.3), 1.80 (1H, ddq, *J* = 13.7, 11.9, 7.1), 2.17 (1H, dqd, *J* = 13.7, 7.1, 4.4), 2.92 (3H, s), 3.21 (1H, ddd, *J* = 8.7, 4.8, 3.0), 3.79 (3H, s), 5.65 (1H, dd, *J* = 10.5, 4.9), 6.12 (1H, d, *J* = 10.5), 6.23 (1H, d, *J* = 7.5), 6.60 (1H, dd, *J* = 8.9, 2.9), 6.79−6.90 (3H, m), 6.93−7.04 (3H, m), 7.21−7.26 (2H, m), 7.33−7.43 (3H, m); rotameric peaks 0.90 (3H, t), 2.05 (1H, m), 3.32 (1H, m), 3.81 (3H, s), 6.02 (1H, m), 6.65 (1H, m), 7.21−7.26 (1H, m), 7.33−7.43 (2H, m); ^{13}C NMR δ 12.2 (CH_3), 21.2 (CH_3), 23.0 (CH_2), 48.0 (CH), 63.2 (CH), 91.7 (CH), 114.9 (CH), 113.8 (CH), 116.3 (q, *J* = 288.8, CF_3), 128.1 (CH), 128.2 (CH), 128.9 (CH), 129.2 (CH) 129.3 (2 × CH), 129.4 (CH), 129.5 (*C*), 129.6 (CH), 129.8 (CH), 130.2 (CH), 130.4 (*C*), 130.5 (CH), 132.3 (CH), 139.0 (*C*), 139.4 (CH), 158.2 (q, *J* = 35.8, *C*═O), 160.3 (*C*); rotameric peaks 12.5 (CH_3), 26.4 (CH_2), 48.2 (CH), 90.8 (CH); ^{19}F NMR ($CDCL_3$, 376 MHz) δ − 67.1 (3F, s, CF_3); *m*/*z* (ESI$^+$) 523 (91, M + Na$^+$), 518 (94, M + NH_4^+), 501 (11, M + H$^+$); HRMS $C_{27}H_{27}F_3N_2NaO_4$ calcd 523.1815, found 523.1801, $C_{27}H_{31}F_3N_3O_4$ calcd 518.2261, found 518.2247, $C_{27}H_{28}F_3N_2O_4$ calcd 501.1996, found 501.1988; HPLC measured for parent nitroalkane obtained via retro-addition (Chiracel OD-H 150 mm column with guard, 98:2 hexane/EtOH, 0.5 mL min^{-1}) 11.5 min (major), 14.4 min (minor) shows 86% ee.

*Entry 4: Cu(**7**)$_2$OTf, THF, or PhMe.* Isolated as a single diastereoisomer as a yellow oil (220 mg, 68%): R_f 0.28 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ +53.1 (*c* 0.72, $CHCl_3$); IR ν_{max} 3053, 2986, 2306, 1691, 1608, 1551, 1512, 1260 cm^{-1}; ^{1}H NMR δ 0.72 (3H, t, *J* = 7.3), 0.82 (3H, t, *J* = 7.3), 0.86−1.07 (6H, m), 1.68 (4H, m), 3.12 (1H, td, *J* = 10.3, 4.0), 3.84 (3H, s), 4.23 (1H, m) 5.23 (1H, dd, *J* = 10.2, 3.9), 6.86 (2H, m), 7.00 (2H, m), 7.19 (2H, m), 7.32 (1H, m), 7.38 (2H, m); ^{13}C NMR δ 11.4 (CH_3), 13.9 (CH_3), 22.1 (CH_2), 23.7 (CH_2), 26.0 (CH_2), 27.1 (CH_2), 31.2 (CH_2), 49.2 (CH), 55.4 (CH_3), 61.1 (CH), 92.7 (CH), 113.9 (CH), 114.3 (CH), 116.1 (q, *J* = 288.6, CF_3), 117.5 (*C*) 127.8 (*C*), 128.0 (CH), 128.3 (2CH), 129.0 (2CH), 130.9 (CH), 131.2 (CH), 137.4 (CH), 158.3 (q, *J* = 35.5, *C*═O), 160.3 (*C*); ^{19}F ($CDCl_3$, 376 MHz) δ − 67.3 (3F, s, CF_3); *m*/*z* (ESI$^+$) 503 (M + Na$^+$, 100), 498 (M + NH_4^+, 79), 481 (M + H$^+$, 3); HRMS $C_{25}H_{31}F_3N_2NaO_4$ calcd 503.2128, found 503.2128, $C_{25}H_{35}F_3N_3O_4$ calcd 498.2574, found 498.2571, $C_{25}H_{32}F_3N_2O_4$ calcd 481.2309, found 481.2326; HPLC measured for parent nitroalkane obtained via retro-addition (Chiracel OD-H 150 mm column with guard, 98:2 hexane/EtOH, 0.5 mL min^{-1}) 12.7 min (min), 15.6 min (major) shows 90% ee.

*Entry 5: Ligand **8**, THF.* Isolated as a single diastereoisomer as a white crystalline solid (220 mg, 69%): mp 179−182 °C; R_f 0.11 (10% acetone/petroleum ether); $[\alpha]^{16}_D$ +27.2 (*c* 0.72, CH_2Cl_2); IR ν_{max} (thin film) 3033, 2968, 2879, 1696, 1555, 1367, 1208, 1159, 1181, 839, 745, 701 cm^{-1}; ^{1}H NMR δ 0.70 (3H, t, *J* = 7.3), 1.70 (1H, ddq, *J* = 14.3, 11.5, 7.2), 1.86 (1H, dqd, *J* = 13.4, 7.3, 3.1), 3.13 (1H, ddd, *J* = 11.3, 8.5, 3.1), 3.75 (3H, s), 5.64 (1H, apt t, *J* = 8.1), 5.89 (1H, d, *J* = 11.0), 6.20 (1H, dd, *J* = 3.3, 1.8), 6.29 (2H, m), 6.55 (1H, m), 6.79 (1H, dd, *J* = 8.7, 2.2), 7.04 (2H, m), 7.22−7.36 (5H, m); ^{13}C NMR δ 11.7 (CH_3), 24.8 (CH_2), 48.2 (CH), 55.4 (CH_3), 57.8 (CH), 90.1 (CH), 111.0 (CH), 113.5 (2 CH), 113.6 (CH), 114.0 (CH), 115.9 (q, *J* = 288.5, CF3), 127.9 (*C*), 128.0 (2 CH), 129.0 (2 CH), 130.4 (CH), 130.9 (CH), 137.8 (*C*), 142.7 (*C*), 145.0 (CH), 157.8 (q, *J* = 33.8, *C*═O), 160.1 (*C*); ^{19}F ($CDCl_3$, 282 MHz) δ −68.0 (3F, s, CF_3); *m*/*z* (CI$^+$) 477 (MH$^+$, 34); HRMS $C_{24}H_{24}F_3N_2O_5$ calcd 477.16372, found 477.16435; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 16.1 min (major), 19.8 min (minor) shows 92% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

*Entry 6: Ligand **8**, THF.* Isolated as a single diastereoisomer as a yellow oil (244 mg, 74%): R_f 0.24 (15% Et_2O/petroleum ether): $[\alpha]^{16}_D$ +16.7 (*c* 0.54, CH_2Cl_2); IR ν_{max} (thin film) 2973, 2840, 1699, 1554, 1511, 1255, 1208, 1181, 839, 700 cm^{-1}; ^{1}H NMR δ 0.76 (3H, t, *J* = 7.2), 1.74 (1H, ddq, *J* = 13.7, 11.5, 7.4), 1.94 (1H, dqd, *J* = 13.7, 7.3, 3.1), 3.14 (1H, ddd, *J* = 10.9, 7.0, 3.1), 3.77 (3H, s), 5.78 (1H, dd, *J* = 8.5, 7.2), 6.03 (1H, d, *J* = 8.5), 6.40 (1H, m), 6.63 (2H, m), 6.80 (2H, m), 6.93 (1H, m), 7.12 (2H, d, *J* = 7.3), 7.16−7.37 (4H, m); ^{13}C NMR δ 11.8 (CH_3), 24.0 (CH_2), 48.3 (CH), 55.5 (CH_3), 60.1 (CH), 92.1 (CH), 113.7 (CH), 114.1 (CH), 116.1 (q, *J* = 288.9, CF_3), 126.4 (*C*), 126.6 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.9 (CH), 129.4 (CH), 130.5 (CH), 131.3 (CH), 133.5 (*C*), 136.4.0 (CH), 138.6 (*C*), 157.9 (q, *J* = 33.5, *C*═O), 160.4 (*C*); minor diastereoisomer −12.2 (CH_3), 23.9 (CH_2), 91.6 (CH), 135.2 (CH), 136.4 (*C*) 138.0 (CH) remaining peaks could not be distinguished; ^{19}F ($CDCl_3$, 282 MHz) δ −68.0 (3F, s, CF_3); *m*/*z* (CI$^+$) 493 (MH$^+$, 53%); HRMS $C_{24}H_{24}F_3N_2O_4S$ calcd 493.14088, found 493.13972; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 18.3 min (major), 20.2 min (minor) shows 95% ee.

*Entry 7: Ligand **8**, THF.* Isolated as a 85:0:15 mixture of diastereoisomers as a yellow solid (241 mg, 72%): mp 102.2−105.7 °C; R_f 0.26 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ −33.5 (c 0.50, $CHCl_3$); IR ν_{max} 2970, 2841, 1697, 1554, 1511, 1254, 1182, 1112 cm^{-1}; ^{1}H NMR δ 0.81 (3H, t, *J* = 7.3), 1.76 (1H, ddq, *J* = 13.5, 11.9, 7.2), 2.16 (1H, dqd, *J* = 13.7, 7.3, 2.9), 2.39 (3H, s), 3.17 (1H, ddd, *J* = 11.8, 4.6, 4.4), 3.81 (3H, s), 5.61 (1H, dd, *J* = 10.4, 4.8), 6.20 (1H, d, *J* = 10.4), 6.21 (1H, d, *J* = 8.0), 6.57 (1H, dd, *J* = 8.8, 2.9), 6.81 (1H, dd, *J* = 8.8, 2.9), 6.90 (1H, td, *J* = 8.8, 2.4), 6.98 (2H, m), 7.10 (2H, m), 7.19 (4H, m); rotameric peaks 0.91 (3H, *J* = 7.3), 2.03 (1H, m), 3.30 (1H, *J* = 10.2, 4.8, 4.0), 3.84 (3H, s), 5.56 (1H, m), 6.10 (1H, dd, *J* = 7.0, 2.2), 6.61 (1H, dd, *J* = 8.9, 2.8), 7.06 (2H, m); ^{13}C NMR δ 12.2 (CH_3), 21.1 (CH_3), 22.9 (CH_2), 47.7 (CH), 55.5 (CH_3), 63.2 (CH), 91.7 (CH), 113.6 (CH), 114.0 (CH), 116.2 (q, *J* = 289.8, CF_3), 127.8 (*C*), 128.1 (CH), 128.6 (CH), 128.8 (CH), 129.6 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 129.7 (CH), 130.5 (CH), 132.2 (CH), 133.3 (CH), 133.3 (*C*), 135.8 (*C*), 137.7 (*C*) 158.2 (q, *J* = 35.3, *C*═O), 160.2 (*C*); rotameric peaks 12.6 (CH_3), 26.4 (CH_2), 47.8 (CH), 137.9 (*C*), 160.4 (*C*); ^{19}F ($CDCl_3$, 376 MHz) δ − 67.1 (3F, s, CF_3); *m*/*z* (ESI$^+$) 523 (M + Na$^+$, 100), 518 (M + NH_4^+, 88), 501 (M + H$^+$, 12); HRMS $C_{27}H_{27}F_3N_2NaO_4$ calcd 523.1815, found 523.1802, $C_{27}H_{31}F_3N_3O_4$ calcd 518.2261, found 518.2250, $C_{27}H_{28}F_3N_2O_4$ calcd 501.1986, found 501.1987. Anal. Calcd for $C_{27}H_{27}F_3N_2O_4$: C, 64.79; H, 5.44; N, 5.60. Found: C, 64.93; H, 5.55; N, 5.38. HPLC measured for parent nitroalkane obtained via retro-addition (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 14.6 min (major), 17.2 min (minor) shows 89% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

*Entry 8: Ligand **8**, THF.* Isolated as a single diastereoisomer as a white solid (195 mg, 62%): mp 121−123 °C; $[\alpha]^{22}_D$ +86.2 (c 0.84, $CHCl_3$); R_f 0.22 (15% Et_2O/petroleum ether); IR ν_{max} (thin flim) 3031, 2978, 1698, 1553, 1511, 1256, 1209, 1181, 840, 700 cm^{-1}; ^{1}H NMR δ 1.59 (3H, d, *J* = 7.1), 3.64 (1H, qd, *J* = 7.7, 4.3), 3.80 (3H, s), 5.69 (1H dd, *J* = 10.9, 4.4), 6.18 (1H, d, *J* = 10.7), 6.24 (1H, m), 6.80−6.91 (2H, m), 7.06 (2H, d, *J* = 7.3), 7.22 (2H, m), 7.28−7.41 (7H, m); ^{13}C NMR δ 15.8 (CH_3), 40.3 (CH), 55. Seven (CH_3), 63.1 (CH), 91.8 (CH), 113.8 (CH), 114.1 (CH), 116.4 (q, *J* = 288.6, CF_3), 127.4 (2 CH), 127.8 (CH), 128.2 (CH), 128.8 (2 CH), 129.5 (CH), 129.6 (CH), 130.4 (CH), 130.6 (CH), 132.3 (CH), 133.7 (*C*), 134.5 (*C*), 141.1 (*C*), 158.3 (q, *J* = 35.4, *C*═O), 160.4 (*C*); ^{19}F ($CDCl_3$, 282 MHz) δ −67.5 (3F, s, CF_3); *m*/*z* (ESI$^+$) 472 (M$^+$, 24); HRMS $C_{25}H_{23}F_3N_2O_4$ calcd 472.16043, found 472.16103. Anal. Calcd For $C_{25}H_{23}F_3N_2O_4$: C, 63.56; H, 4.91; N, 5.93. Found: C, 63.72; H, 4.98; N, 5.89. HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 19.9 min (major), 21.3 min (minor) shows 98% ee.

*Entry 9: Ligand **8**, THF.* Isolated as a single diastereoisomer as a red crystalline solid (236 mg, 74%): mp 121.6−123.0 °C; R_f 0.23 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ +32.3 (*c* 0.76, $CHCl_3$); IR ν_{max} 3011,

2972, 2841, 1698, 1556, 1512, 1255, 1183 cm^{-1}; ^1H NMR δ 0.97 (3H, t, J = 7.3), 1.64 (1H, ddq, J = 14.1, 11.7, 7.2), 2.23 (1H, dqd, J = 13.7, 7.4, 2.6), 3.42 (1H, dt, J = 11.6, 3.2), 3.81 (3H, s), 5.51 (1H, dd, J = 11.4, 3.8), 5.98 (1H, dd, J = 8.8, 1.9), 6.22 (1H, d, J = 3.3), 6.38 (1H, dd, J = 3.3, 1.9), 6.53 (1H, dd, J = 8.8, 2.9), 6.56 (1H, d, J = 1.7), 6.94 (3H, m), 1.17−1.30 (4H, m); ^{13}C NMR δ 12.5 (CH_3), 21.2 (CH_2), 41.9 (CH), 55.5 (CH_3), 60.0 (CH), 88.8 (CH), 108.2 (CH), 110.7 (CH), 113.8 (CH), 113.8 (CH), 115.7 (q, J = 287.5, CF_3), 126.5 (C), 128.6 (CH), 128.8 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 130.5 (CH), 130.5 (CH), 133.0 (CH), 133.4 (C), 142.3 (CH), 152.0 (CH), 158.2 (q, J = 35.9, C═O), 160.3 (C); ^{19}F ($CDCl_3$, 376 MHz) δ −66.9 (3F, s, CF_3); m/z (ESI^+) 499 ($M + Na^+$, 100), 494 ($M + NH_4^+$, 38), 477 ($M + H^+$, 11); HRMS $C_{24}H_{23}F_3N_2NaO_5$ calcd 499.1451, found 499.1438, $C_{24}H_{27}F_3N_3O_5$ calcd 494.1897, found 494.1883, $C_{24}H_{24}F_3N_2O_5$ calcd 477.1632, found 477.1635. Anal. Calcd for $C_{24}H_{23}F_3N_2O_5$: C, 60.50; H, 4.87; N, 5.88. Found: C, 60.75; H, 4.90; N, 5.66. HPLC (Chiracel OD-H 250 mm column with guard 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}), 19.5 (major), 22.2 (minor) shows 89% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

Entry 10: Ligand ***8****, THF.* Isolated as a 90:0:10 mixture of diastereoisomers as a white crystalline solid (264 mg, 80%): mp 132−234 °C; $[\alpha]^{16}_D$ +25.4 (c 0.66, CH_2Cl_2); R_f 0.13 (8% acetone/petroleum ether); IR ν_{max} (thin film) 3065, 2971, 2877, 1698, 1553, 1362, 1208, 1168, 839, 699 cm^{-1}; ^1H NMR δ 0.96 (3H, t, J = 7.1), 1.72 (1H, ddq, J = 13.7, 11.7, 7.1), 2.37 (1H, dqd, J = 13.7, 7.3, 2.6), 3.53 (1H, dt, J = 11.6, 3.6), 3.81 (3H, s), 5.54 (1H dd, J = 11.0, 3.6), 6.11 (1H, m), 6.41 (1H, d, J = 11.0), 6.58 (1H, dd, J = 8.9, 2.9), 6.86−6.95 (2H, m), 6.98−7.13 (3H, m), 7.22 (2H, m), 7.26−7.37 (3H, m); ^{13}C δ 12.6 (CH_3), 24.0 (CH_2), 43.1 (CH), 55.5 (CH_3), 61.5 (CH), 91.6 (CH), 113.8 (CH), 114.2 (CH), 116.2 (q, J = 286, CF_3), 124.7 (CH), 125.7 (CH), 127.0 (C), 127.4 (CH), 128.8 (2 CH), 12.3 (2 CH), 129.5 (CH), 130.5 (CH), 132.6 (CH), 133.3 (C), 142.0 (C), 158.3 (q, J = 35, C═O), 160.4 (C); ^{19}F ($CDCl_3$, 282 MHz) δ − 67.5 (3F, s, CF_3); m/z (FAB^+) 493 (MH^+, 41); HRMS $C_{24}H_{24}F_3N_2O_4S$ calcd 493.14089, found 493.14149. Anal. Calcd for $C_{24}H_{23}F_3N_2O_4S$: C, 58.53; H, 4.71; N, 5.69. Found: C, 58.57; H, 4.70; N, 5.63. HPLC measured for parent nitroalkane obtained via retro-addition (Chiracel OD-H 250 mm column with guard, 99:1 hexane/IPA, 0.5 mL min^{-1}) 37.4 min (major), 38.4 min (minor) shows 90% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

Entry 11: Ligand ***8****, THF.* Isolated as a single diastereoisomer as a yellow oil (246 mg, 73%): R_f 0.18 (10% EtOAc/petroleum ether); $[\alpha]^{22}_D$ +24.8 (c 0.49, $CHCl_3$); IR ν_{max} 3010, 2965, 2840, 1698, 1607, 1585, 1553, 1512, 1254, 1112 cm^{-1}; ^1H NMR δ 0.80 (3H, t, J = 7.3), 1.71 (1H, qdd, J = 14.3, 11.9, 7.1), 2.13 (1H, dqd, J = 14.2, 7.1, 2.9), 3.14 (1H, ddd, J = 11.8, 4.8, 3.0), 3.77 (3H, s), 3.82 (3H, s), 5.62 (1H, dd, J = 10.4, 4.9), 6.15 (2H, m), 6.56 (1H, dd, J = 8.8, 2.9), 6.81 (1H, dd, J = 8.8, 2.9), 6.88−6.97 (6H, m), 7.15 (2H, dt, J = 8.7, 3.1), 7.20 (2H, t, J = 7.7), 7.28 (1H, tt, J = 7.7, 3.1); ^{13}C NMR δ 12.2 (CH_3), 23.2 (CH_2), 47.2 (CH), 55.2 (CH_3), 55.4 (CH_3), 63.2 (CH), 91.7 (CH), 113.6 (CH), 114.1 (CH), 114.3 (2CH), 116.2 (q, J = 290.1, CF_3), 127.7 (C), 128.6 (CH), 128.7 (CH), 129.2 (CH), 129.4 (2CH), 129.7 (CH), 130.5 (C), 130.7 (CH), 132.2 (CH), 132.3 (C), 133.2 (CH), 158.0 (q, J = 35.8, C═O), 159.2 (C), 160.2 (C); ^{19}F ($CDCl_3$, 376 MHz) δ −67.2 (3F, s, CF_3); m/z (ESI^+) 539 ($M + Na^+$, 68), 534 ($M + NH_4^+$, 61), 517 ($M + H^+$, 6); HRMS $C_{27}H_{27}F_3N_2NaO_5$ calcd 539.1764, found 539.1747, $C_{27}H_{31}F_3N_3O_5$ calcd 534.2210, found 534.2202, $C_{27}H_{28}F_3N_2O_5$ calcd 517.1945, found 517.1935; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 18.3 min (major), 22.8 min (minor) shows 90% ee.

Entry 12: No Ligand, THF. Isolated as a 90:0:10:0 mixture of diastereoisomers as a colorless oil (136 mg, 38%): R_f 0.20 (15% Et_2O/petroleum ether); IR ν_{max} (thin film) 3079, 2971, 2841, 1695, 1552, 1509, 1347, 1253, 1207, 732, 699 cm^{-1}; ^1H NMR δ 0.83 (3H, t, J = 7.3), 1.81 (1H, ddq, J = 14.1, 11.9, 7.1), 2.21 (1H, dqd, J = 14.3, 7.3, 2.8), 3.32 (1H, ddd, J = 11.8, 4.3, 3.1), 3.79 (3H, s), 5.77 (1H, dd, J = 10.1, 4.5), 5.88 (1H, d, J = 9.9), 6.34 (1H, d, J = 7.7), 6.63 (1H, dd, J = 8.8, 2.3), 6.84 (2H, m), 7.00 (2H, d, J = 7.6), 7.20 (2H, d, J = 7.7), 7.30 (1H, t, J = 7.5), 7.38 (2H, d, J = 8.7), 8.24 (2H, d, J = 8.8); ^{13}C NMR δ 12.2 (CH_3), 22.7 (CH_2), 47.7 (CH), 55.6 (CH_3), 64.4 (CH), 91.1 (CH), 112.7 (CH), 113.9 (CH), 116.1 (q, J = 288.6, CF_3), 124.2 (2 CH), 128.9 (2 CH), 129.3 (2 CH), 129.6 (C), 129.8 (2 CH), 130.4 (CH), 131.6 (CH), 132.9 (CH), 145.0 (C), 146.3 (C), 147.7 (C), 158.3 (q, J = 35.8, C═O), 160.1 (C); ^{19}F ($CDCl_3$, 282 MHz) δ − 67.7 (3F, s, CF_3); m/z (EI^+) 531 (M^+, 68); HRMS $C_{26}H_{24}F_3N_3O_6$ calcd 531.16117, found 531.16121.

Entry 26: Ligand ***8****, PhMe.* Isolated as a yellow crystalline solid (178 mg, 69%): mp 108−109 °C; R_f 0.19 (15% Me_2CO/hexanes); $[\alpha]^{25}_D$ −28.4 (c 0.83, $CHCl_3$); IR ν_{max} 3410, 2962, 1740, 1556 cm^{-1}; ^1H NMR δ 0.72 (3H, t, J = 7.4), 1.41 (3H, t, J = 7.2), 1.65 (2H, m), 3.57 (1H, ddd, J = 11.6, 8.4, 6.8), 3.74 (3H, s), 4.06 (1H, d, J = 2.8), 4.27 (1H, dq, J = 10.6, 7.2), 4.33 (1H, dq, J = 10.6, 7.2), 5.08 (1H, dd, J = 11.6, 2.4), 6.25 (2H, m), 6.71 (2H, m), 7.35 (3H, m), 7.48 (2H, m); ^{13}C NMR δ 11.5 (CH_3), 14.1 (CH_3), 25.8 (CH_2), 47.1 (CH), 55.7 (CH_3), 58.6 (CH), 62.5 (CH_2), 94.3 (CH), 114.9 (2CH), 116.0 (2CH), 128.1 (CH), 128.9 (2CH), 129.1 (2CH), 138.0 (C), 138.1 (C), 153.6 (C), 168.5 (C═O); m/z (EI+) 472 (100), 368 (67), 387 (58, MH^+) 409 (29, MNa^+); HRMS $C_{21}H_{27}N_2O_5$ calcd 387.1914, found 387.1097; HPLC (Chiracel OD-H 250 mm column with guard, 99:1 hexane/IPA, 0.5 mL min^{-1}), 22.2 (minor), 28.6 (major) shows 95% ee.

Entry 13: No Ligand, THF. Isolated as a 5:0:0:95 mixture of diastereoisomers as an off-white solid (141 mg, 38%): mp 57−59 °C; R_f 0.18 (10% EtOAc/petroleum ether); IR ν_{max} 2981, 2844, 1696, 1585, 1511, 1311, 1181 cm^{-1}; ^1H NMR δ 0.81 (3H, t, J = 7.4), 1.84−2.07 (2H, m), 3.76, (3H, s), 3.83 (1H, td, J = 9.1, 4.6), 5.94 (1H, d, J = 8.7), 6.16 (1H, t, J = 8.7), 6.23 (1H, dd, J = 8.8, 2.2), 6.57 (1H, dd, J = 8.9, 2.8), 6.80 (2H, m), 7.17−7.35 (5H, m), 7.39 (1H, t, J = 7.1), 7.56 (2H, m), 7.68 (1H, d, J = 8.0); ^{13}C NMR δ 10.8 (CH_3), 26.7 (CH_2), 43.0 (CH), 55.5 (CH_3), 65.6 (CH), 89.6 (CH), 113.5 (CH), 114.1 (CH), 116.1 (q, J = 288.3, CF_3C═O), 124.2 (q, J = 274.0, CF_3Ar), 126.7 (q, J = 6.13, CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.4 (C), 128.6 (CH), 129.6 (CH), 129.7 (q, J = 39.9, $ArCF_3$), 129.7 (q, J = 33.7, CH), 130.5 (CH), 130.9 (CH), 131.9 (CH), 132.3 (CH), 132.8 (C), 138.0 (C), 158.4 (q, J = 35.8, C═O), 160.2 (C); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −67.6 (3F, s, CF_3C═O), −57.4 (3F, s, CF_3Ar); m/z (ESI^+) 572 (100, MNH_4^+), 577 (64, MNa^+), 555 (6, MH^+); HRMS $C_{27}H_{25}F_6N_2O_4$ calcd 555.1713, found 555.1695, $C_{27}H_{28}F_6N_3O_4$ calcd 572.1979, found 572.1956, $C_{27}H_{24}F_6N_2NaO_4$ calcd 577.1532, found 577.1512. X-ray structure confirmed relative stereochemistry (Supporting Information).

Entry 14: No Ligand THF. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 50:0:50:0. Isolated as two separate single diastereoisomers as white solids (8 mg each, 4% in total): mp 119−123 °C; R_f 0.20 (15% Et_2O/petroleum ether); IR ν_{max} (thin film) 2968, 1698, 1551, 1512, 1245, 1207, 1182, 757, 733 cm^{-1}; in order of elution ^1H NMR δ 0.80 (3H, t, J = 7.2), 1.84 (1H, ddq, J = 13.8, 7.2, 6.7), 2.34 (1H, brs), 3.78 (3H, s), 3.90 (1H, m), 3.93 (3H, s), 5.48 (1H, apt. d, J = 8.6), 6.06 (1H, d, J = 8.1), 6.53 (2H, m), 6.84 (1H, dd, J = 8.8, 2.7), 6.93−7.00 (4H, m), 7.07 (1H, d, J = 7.4), 7.16 (2H, t, J = 7.5), 7.24−7.35 (3H, m); ^{13}C NMR δ 12.2 (CH_3), 21.4 (CH_2), 44.6 (CH), 55.3 (O*Me*), 55.5 (CH_3), 61.4 (CH), 90.2 (CH), 110.7 (CH), 113.6 (CH), 113.7 (CH), 116.4 (q, J = 287.9, CF_3), 121.2 (CH), 127.0 (C), 127.4 (CH), 128.5 (2xCH), 128.7 (CH), 129.2 (2xCH), 129.4 (2xCH), 130.8 (CH), 132.9 (C), 133.5 (C), 157.0 (C), 158.0 (q, J = 33.3, C═O), 160.2 (C); then ^1H NMR ($CDCl_3$, 600 MHz, 327 K) δ 0.86 (3H, t, J = 7.3, *CH*3), 1.90 (1H, brs), 1.98 (1H, dqd, J = 14.4, 7.3, 5.2), 3.79 (3H, s), 3.81 (3H, s), 4.15 (1H, brs), 5.74 (1H, brs), 5.93 (1H, brs), 6.60 (1H, d, J = 8.4), 6.81−6.98 (3H, m), 7.08 (2H, m), 7.16 (1H, m), 7.19 (2H, t, J = 7.8), 7.26 (2H, m), 7.33 (1H, m), 7.46

(1H, m); ^{13}C NMR δ 11.5 (CH_3), 29.5 (CH_2), 37.4 (CH), 55.6 (CH_3), 55.9 (CH_3), 62.9 (CH), 90.7 (CH), 111.0 (CH), 113.9 (CH), 114.2 (CH), 114.8 (2 × CH), 116.8 (q, J = 289.0, CF_3), 121.1 (2 × CH), 122.5 (2 × CH), 126.0 (C), 128.7 (2 × CH), 129.1 (CH), 129.3 (CH), 130.9 (C), 135.7 (C), 158.1 (q, J = 35.5, C═O), 158.4 (C), 160.5 (C); ^{19}F ($CDCl_3$, 282 MHz) δ −67.7 (3F, s, CF_3); m/z (EI$^+$) 516 (M^+, 6); HRMS $C_{27}H_{27}F_3N_2O_5$ calcd 516.18666, found 516.18646.

General Procedure for the Synthesis of *syn,syn*-β-Nitroamines (Table 4) (b). *Using Cu(**7**)$_2$OTf and Et$_2$O.* To a stirred mixture of nitroalkene (1.00 mmol), Cu(7)$_2$OTf (0.05 mmol), and pivalamide (0.80 mmol) in Et_2O (5 mL) at −70 °C was added R_2Zn (1.1 mmol, 1 M in hexanes) dropwise. The mixture was stirred at this temperature until the reaction was complete by TLC analysis (approximately 20 h). A solution of imine (2.0 mmol) in dry Et_2O (2 mL) was added and the mixture stirred for 20 min. A solution of TFA (3.5 mmol) in Et_2O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 2 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid in a vivid yellow supernatant. The reaction was quenched by the addition of Et_2O and saturated aq $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with Et_2O. The organic layers were combined, and the solvent was removed in vacuo to provide crude β-nitroamine. Note: $MgSO_4$ was not used to dry the product β-nitroamines prior to solvent removal because the products were found to be mildly unstable toward this reagent. Diastereoselectivities were calculated by comparison of the ^{1}H NMR signals for the C*H*CHNO$_2$ protons (~3.1−3.6 ppm). Purification by flash chromatography yielded diastereomerically pure (1*S*,2*S*,3*R*)-*syn,syn*-β-nitroamines **b** (Table 4, entries 15, 17−19).

*Using Ligand **8** and PhMe.* Ligand **8** (0.02 mmol) and $(CuOTf)_2\cdot$PhMe (0.01 mmol) were added to a flame-dried flask in a glovebox and the flask equipped with a septum. The flask was removed from the glovebox and dry PhMe (2 mL) added. The suspension was stirred at rt for 10 min to provide a yellow solution. The solution was cooled to −30 °C and stirred for 10 min before $ZnEt_2$ (1.1 mmol, 1 M in hexanes) was added dropwise and stirred for 10 min to provide an orange solution. A solution of nitroalkene (1 mmol) in PhMe (1 mL) was added dropwise over 20 s and stirred for 20 min before warming to rt to provide a yellow solution. The reaction was stirred at rt until complete by tlc analysis (approx 16 h). The reaction was then cooled to −78 °C and then proceeded as above to yield diastereomerically pure (1*R*,2*R*,3*S*)-*syn*, *syn*-β-nitroamines **b** (Table 4, entries 16, 20−24).

*Entry 15: Cu(**7**)$_2$OTf, Et$_2$O.* Isolated as a yellow crystalline solid (162 mg, 62%): mp 129−131 °C; R_f 0.20 (20% Me_2CO/hexanes); $[\alpha]^{25}_D$ +2.8 (c 0.75, $CHCl_3$); IR ν_{max} 3414, 2935, 1552 cm^{-1}; ^{1}H NMR δ 0.75 (3H, t, J = 7.2), 1.66 (1H, dqd, J = 13.5, 7.2, 3.7), 1.79 (1H, ddq, J = 13.5, 11.6, 7.2), 3.61 (1H, app. td, J = 11.3, 3.6), 3.68 (3H, s), 4.23 (1H, dd, J = 10.5, 3.5), 4.94 (1H, dd, J = 11.1, 3.6), 5.09 (1H, d, J = 10.5), 6.29 (2H, m), 6.63 (2H, m), 7.08 (2H, m), 7.22 (5H, m), 7.33 (3H, m); ^{13}C NMR δ 11.7 (CH_3), 25.1 (CH_2), 48.0 (CH), 55.6 (CH_3), 57.1 (CH), 98.9 (CH), 114.4 (2C, C*H*), 114.7 (2C, C*H*), 126.1 (2C, C*H*), 127.6 (C*H*), 128.0 (C*H*), 128.4 (C*H*), 128.8 (2C*H*), 128.9 (C*H*), 129.1 (2C, C*H*), 138.1 (C), 138.3 (C), 140.1 (C), 152.2 (C); m/z (EI+) 391 (100, MH^+), 340 (4.5); HRMS $C_{24}H_{27}N_2O_3$ calcd 391.2016, found 391.2004. Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.91; N, 7.17. Found: C, 73.80; H, 6.63; N, 7.15. HPLC of parent nitroalkane from degradation, (Chiralcel OD-H 150 mm column with guard, 98:2 hexane/EtOH, 0.5 mL min^{-1}), 24.2 min (major), 34.6 (minor), shows 90% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

*Entry 16: Ligand **8**, PhMe.* Isolated as a single diastereoisomer as a pale yellow oil (182 mg, 72%): $[\alpha]^{16}_D$ +11.4 (c 0.67, CH_2Cl_2); R_f 0.31 (15% acetone/petroleum ether); IR ν_{max} (thin film) 3061, 3029, 1549, 1509, 1242, 819, 699 cm^{-1}; ^{1}H NMR δ 1.37 (3H, d, J = 7.0), 3.68 (3H, s), 3.87 (1H, qd, J = 10.9, 6.9), 4.26 (1H, dd, J = 10.6, 3.7), 4.88 (1H, dd, J = 10.9, 3.8), 5.11 (1H, d, J = 10.5), 6.31 (2H, m), 6.64 (2H, m), 7.06 (2H, m), 7.17−7.35 (8H, m); ^{13}C NMR δ 18.3 (CH_3), 40.6 (CH), 55.7 (CH_3), 57.1 (CH), 99.7 (CH), 114.5 (2 × CH), 114.8 (2 × CH), 126.2 (CH2 ×), 127.8 (CH2 ×), 127.9 (CH), 128.1 (CH), 129.0 (2 × CH), 129.2 (2 × CH), 138.3 (C), 140.0 (C), 140.3 (C), 152.3 (C); m/z (EI$^+$) 376 (M^+, 64); HRMS $C_{23}H_{24}N_2O_3$ calcd 376.17814, found 376.17834; HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 26.3 min (major), 28.8 min (minor) shows 93% ee.

*Entry 17: Cu(**7**)$_2$OTf, Et$_2$O.* Isolated as a yellow crystalline solid (198 mg, 70%): mp 93−95 °C; R_f 0.28 (20% Me_2CO/hexanes); $[\alpha]^{25}_D$ +33.8 (c 0.97, $CHCl_3$); IR ν_{max} 3423, 3007, 1552, 1242 cm^{-1}; ^{1}H NMR δ 0.74 (3H, t, J = 7.2), 1.65 (1H, dqd, J = 13.5, 7.2, 3.5), 1.77 (1H, ddq, J = 13.5, 11.4, 7.2), 3.60 (1H, apt. td. J = 11.3, 3.5), 3.69 (3H s), 4.18 (1H, d, J = 3.4), 4.91 (1H, dd, J = 11.1, 3.5), 6.25 (2H, m), 6.63 (2H, m), 7.00 (2H, m), 7.23 (4H, m), 7.50 (3H, m); ^{13}C NMR δ 11.6 (CH_3), 25.1 (CH_2), 48.0 (CH), 55.6 (CH_3), 56.6 (CH), 98.6 (CH), 114.6 (2CH), 114.8 (2CH) 127.5 (2CH), 127.8 (CH), 128.4 (CH), 129.1 (2C, CH), 129.2 (2CH), 133.8 (CH)136.8 (C), 137.9 (C), 138.1 (C), 139.6 (C), 152.4 (C); m/z (EI+) 425 (100, MH^+), 427 (36), 413 (29), 362 (16); HRMS $C_{24}H_{26}N_2O_3Cl$ calcd 425.1626, found 425.1625; HPLC of parent nitroalkane from degradation (Chiralcel OD-H 150 mm column with guard, 98:2 hexane/IPA, 0.5 mL min^{-1}), 14.7 min (major), 20.2 (minor), shows 91% ee.

*Entry 18: Cu(**7**)$_2$OTf, Et$_2$O.* Isolated as a yellow crystalline solid (189 mg, 70%): mp 87−88 °C; R_f 0.31 (25% Et_2O/hexanes); $[\alpha]^{25}_D$ +16.6 (c 0.91, $CHCl_3$); IR ν_{max} 3414, 3009, 1552, 1513 cm^{-1}; ^{1}H NMR δ 0.73 (3H, t, J = 7.3), 1.66 (1H, dqd, J = 13.2, 7.3, 3.6), 1.78 (1H, apt. qt, J = 13.4, 7.3), 2.28 (3H, s), 3.61 (1H, apt. td, J = 11.4, 3.6), 3,68 (3H, s), 4.20 (1H, bd, J = 3.2), 4.94 (1H, dd, J = 11.1, 3.6), 5.08 (1H, b), 6.28 (2H, d, J = 8.9), 6.62 (2H, m), 6.95 (2H, d, J = 8.1), 7.05 (2H, d, J = 8.0), 7.22 (2H, m), 7.31 (3H, m); ^{13}C NMR δ 11.6 (CH_3), 21.1 (CH_3) 25.1 (CH_2), 48.0 (C*H*), 55.6 (CH_3), 56.8 (CH), 99.0 (CH), 114.7 (2C*H*), 114.7 (2C, C*H*), 126.0 (2C, C*H*), 127.7 (C*H*), 128.4 (2C*H*), 129.1 (2C*H*), 129.6 (2C*H*), 133.13 (C), 137.7 (C), 138.2 (C), 140.1 (C), 152.2 (C); m/z (EI+) 405 (100, MH^+), 427 (88, $C_{18}H_{19}NO_2Na^+$), 270 (50, $C_{18}H_{20}NO_2^+$); HRMS $C_{25}H_{29}N_2O_3$ calcd 405.2173, found 405.2160. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found C, 74.33; H, 7.04; N, 7.08%; HPLC (Chiracel OD-H 150 mm column with guard, 99:1 hexane/EtOH, 0.4 mL min^{-1}), 12.7 (minor), 13.7 (major) shows 95% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

*Entry 19: Cu(**7**)$_2$OTf, Et$_2$O.* Isolated as a red solid (183 mg, 72%): mp 105−108 °C; R_f 0.37 (10% acetone/petroleum ether); $[\alpha]^{22}_D$ −21.3 (c 0.70, $CHCl_3$); IR ν_{max} 3380, 2966, 2933, 2834, 1551, 1511, 1364, 1242 cm^{-1}; ^{1}H NMR δ 0.75 (3H, t, J = 7.3), 1.68 (1H, dqd, J = 13.6, 7.3, 3.7), 1.80 (1H, ddq, J = 13.6, 11.5, 7.3), 3.57 (1H, app. td, J = 11.2, 3.7), 3.73 (3H, s), 4.36 (1H, dd, J = 11.2, 3.8), 4.58 (1H, d, J = 11.2), 5.20 (1H, dd, J = 11.0, 3.9), 6.02 (1H, d, J = 3.3), 6.19 (1H, dd, J = 3.3, 1.8), 6.30−6.34 (2H, m), 6.66−6.70 (2H, m), 7.20−7.22 (2H, m), 7.27−7.34 (4H, m); ^{13}C NMR δ 11.6 (CH_3), 25.3 (CH_2), 47.5 (CH), 53.0 (CH) 55.5 (CH_3), 95.6 (CH), 108.0 (CH), 110.5 (CH), 114.7 (3C, CH), 115.3 (2C, CH), 127.7 (CH), 128.6 (CH), 129.0 (2C, CH), 137.9 (C), 140.0 (CH), 142.5 (C), 151.6 (C), 152.8 (C); HRMS $C_{22}H_{24}N_2O_2$ calcd 380.1731, found 380.1740; HPLC (Chiracel OD-H 250 mm column with guard 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}), 22.5 (major), 28.7 (minor) shows 92% ee.

*Entry 20: Ligand **8**, PhMe.* Isolated as a single diastereoisomer as a yellow solid (199 mg, 65%): mp 127−130 °C; $[\alpha]^{22}_D$ +9.5 (c 0.34, DCM) Rf 0.14 (15% acetone/petroleum ether); IR ν_{max} (thin film) 3067, 2967, 2933, 1551, 1511, 1243, 1037, 820, 701 cm^{-1}; ^{1}H NMR δ 0.73 (3H, t, J = 7.3), 1.67 (1H, dqd, J = 13.4, 7.3, 3.7), 1.80 (1H, ddq, J = 13.4, 11.6, 7.2), 3.58 (1H, td, J = 11.3, 3.5), 3.70 (3H, s), 4.50 (1H, dd, J = 10.3, 3.5), 4.92 (1H, d, 10.7), 5.06 (1H, dd, J = 10.9, 3.7), 6.32 (2H, m), 6.66 (2H, m), 6.80 (1H), 6.86 (1H, m), 7.13 (1H, m), 7.18 (2H, m), 7.30 (3H, m); ^{13}C NMR δ 11.5 (CH_3), 24.8 (CH_2), 47.5 (CH), 53.7 (CH),

55.2 (CH_3), 98.2 (CH), 114.1 (2 × CH), 114.7 (CH2 ×), 122.0 (CH), 124.3 (CH), 124.6 (CH), 126.6 (CH), 127.3 (CH), 128.1 (CH), 131.2 (2 × CH), 137.5 (*C*), 139.5 (*C*), 142.4 (*C*), 154.3 (*C*); *m*/*z* (EI^+) 396 (M^+, 8); HRMS $C_{22}H_{24}N_2O_3S$ calcd 396.15021, found 396.14952; HPLC (Chiracel OD-H 150 mm column, 99.5:0.5 hexane/IPA, 0.5 mL min^{-1}) 21.0 min (major), 24.8 min (minor) shows 95% ee.

Entry 21: Ligand ***8****, PhMe.* Isolated as a yellow crystalline solid (186 mg, 69%): mp 86−88 °C; R_f 0.22 (20% Me_2CO/hexanes); $[\alpha]^{25}_D$ −5.1 (*c* 0.74, $CHCl_3$); IR ν_{max} 3421, 2935, 1552, 1240 cm^{-1}; ^1H NMR δ 0.74 (3H, t, *J* = 7.3), 1.61 (1H, dqd, *J* = 13.5, 7.3, 3.6), 1.75 (1H, apt. qt, *J* = 13.4, 7.3), 3.36 (3H, s), 3.58 (1H, apt. td, *J* = 11.3, 3.6), 3.69 (3H, s), 4.25 (1H, dd, *J* = 10.4, 3.5), 4.91 (1H, dd, *J* = 11.1, 3.6), 5.10 (1H, d, *J* = 10.4), 6.29 (2H, m), 6.62 (2H, m), 7.07 (2H, d, *J* = 6.8), 7.16 (4H, m); ^{13}C NMR δ 11.7 (CH_3), 21.2 (CH_2), 25.0 (CH_3), 47.6 (CH_2), 55.6 (CH_3), 57.0 (CH), 99.1 (CH), 114.7 (2CH), 114.7 (2CH), 126.1 (2CH), 128.0 (CH), 128.3 (CH), 128.3 (CH), 128.9 (2C, CH), 129.8 (2C, CH), 134,9 (*C*), 137.4 (*C*), 138.4 (*C*), 40.1 (*C*), 152.2 (*C*); *m*/*z* (EI+) 405 (100, MH^+), 427 (4, MNa^+); HRMS $C_{25}H_{29}N_2O_3$ calcd 405.2173, found 405.2170. Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.44; H, 7.03; N, 6.93. HPLC (Chiralcel OD-H 150 mm column with guard, 99:1 hexane/EtOH, 0.5 mL min^{-1}), 9.6 min (minor), 10.8 min (major) shows 88% ee.

Entry 22: Ligand ***8****, PhMe.* Isolated as a yellow crystalline solid (166 mg, 71%): mp 119−121 °C; R_f 0.23 (20% Me_2CO/hexanes); $[\alpha]^{25}_D$ −0.3 (*c* 0.82, $CHCl_3$); IR ν_{max} 3421, 3011, 1554, 1513 cm^{-1}; ^1H NMR δ 0.80 (3H, t, *J* = 7.3), 1.57 (1H, dqd, *J* = 13.4, 7.3, 3.7), 1.82 (1H, apt. qt, *J* = 13.4, 7.3), 3.69 (3H, s), 3.73 (1H, apt. td, *J* = 11.0, 3.6), 4.33 (1H, bd, *J* = 4.0), 5.12 (1H, dd, *J* = 10.6, 4.0), 6.13 1H, dd, *J* = 3.2, 0.7), 6.31 (1H, dd, *J* = 3.2, 1.9), 6.41 (2H, m), 6.68 (2H, m), 7.15 (2H, m), 7.26 (4H, m), 7.43 (1H, m); ^{13}C NMR δ 11.5 (CH_3), 23.4 (CH_2), 41.9 (CH), 55.6 (CH_3), 57.9 (CH), 96.0 (CH), 110.0 (CH), 110.5 (CH), 114.8 (2CH), 114.9 (2CH), 126.2 (2CH), 128.1 (CH), 129.8 (2C, CH), 138.0 (*C*), 140.1 (*C*), 142.5 (CH), 150.9 (*C*), 152.4 (*C*); *m*/*z* (EI+) 381 (100, MH^+), 437 (41), 332 (21); HRMS $C_{32}H_{25}N_2O_4$ calcd 381.1809, found 381.1799. Anal. Calcd for $C_{32}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.60; H, 6.40; N, 7.45. HPLC (Chiracel OD-H 150 mm column with guard, 99.5:0.5 Hexane/IPA, 0.4 mL min^{-1}), 19.3 (minor), 22.3 (major) shows 85% *ee*. X-ray structure confirmed relative stereochemistry (Supporting Information).

Entry 23: Ligand ***8****, PhMe.* Isolated as a single diastereoisomer as a yellow solid (204 mg, 77%): mp 122−125 °C; $[\alpha]^{16}_D$ +15.7 (*c* 0.83, DCM); R_f 0.14 (15% acetone/petroleum ether); IR ν_{max} (thin film) 3028, 2967, 2934, 2833, 1551, 1512, 1364, 1242, 819, 699 cm^{-1}; ^1H NMR δ 0.85 (3H, t, *J* = 7.2), 1.70 (2H, m), 3.68 (3H, s), 3.97 (1H, ddd, *J* = 11.0, 8.3, 6.7), 4.36 (1H, d, *J* = 3.5), 4.91 (1H, dd, *J* = 11.0, 3.6), 5.13 (1H, brs), 6.34 (2H, m), 6.64 (2H, m), 6.88 (1H, dd, *J* = 3.5, 1.0), 6.94 (1H, dd, *J* = 5.1, 3.5), 7.09 (2H, m), 7.15 (4H, m); ^{13}C NMR δ 11.6 (CH_3), 26.8 (CH_2), 43.7 (CH), 55.6 (CH_3), 57.1 (CH), 98.9 (CH), 114.8 (2 × H), 125.2 (CH), 126.2 (2 × CH), 127.3 (CH), 127.5 (2 × CH), 128.1 (2 × CH), 129.0 (2 × CH), 138.0 (*C*), 140.1 (*C*), 141.0 (*C*), 152.3 (*C*); *m*/*z* (EI^+) 396 (M^+, 22); HRMS $C_{22}H_{24}N_2O_3S$ calcd 396.15021, found 396.15078. Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.52; H, 6.04; N, 6.96. HPLC (Chiracel OD-H 250 mm column with guard, 99.5:0.5 hexane/IPA, 0.5 mL min-1) 27.2 min (major), 29.3 min (minor) shows 86% ee.

Entry 24: Ligand ***8****, PhMe.* Isolated as a yellow crystalline solid (211 mg, 75%): mp 113−114 °C; R_f 0.26 (20% Me_2CO/hexanes); $[\alpha]^{25}_D$ −12.6 (*c* 0.32, $CHCl_3$); IR ν_{max} 3417, 2967, 1552, 1255 cm^{-1}; ^1H NMR δ 0.74 (3H, t, *J* = 7.2), 1.63 (1H, dqd, *J* = 13.6, 7.2, 3.6), 1.73 (1H, m), 3.58 (1H, apt. td, *J* = 11.6, 3.6), 3.69 (3H, s), 3.82 (3H, s), 4.25 (1H, d, *J* = 3.2), 4.89 (1H, dd, *J* = 10.8, 3.2), 5.11 (1H, b), 6.31 (2H, m), 6.64 (2H, m), 6.86 (2H, m), 7.08 (2H, d, *J* = 6.9), 7.15 (2H, d, *J* = 8.8), 7.25 (3H, m); ^{13}C NMR δ 11.7 (CH_3), 25.0 (CH_2), 47.2 (CH), 55.3 (CH_3), 55.6 (CH_3), 57.0 (CH), 99.2 (CH), 114.5 (2CH), 114.6 (2CH), 114.7 (2CH), 126.1 (2CH), 128.0 (CH), 128.9 (2CH), 129.4 (2CH), 129.9 (*C*), 138.3 (*C*), 140.1 (*C*), 152.2 (*C*), 159.0 (*C*); *m*/*z* (EI+) 421 (100, MH^+), 359 (11); HRMS $C_{25}H_{29}N_2O_4$ calcd 421.2122, found 421.2121. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.43; H, 6.72; N, 6.61. HPLC (Chiracel AD-H 250 mm column with guard, 98:2 hexane/EtOH, 0.5 mL min^{-1}), 23.4 (minor), 33.5 (major) shows 88% ee. X-ray structure confirmed relative stereochemistry (Supporting Information).

Entry 25: No Ligand, Diethylzinc Addition in THF, Nitro-Mannich in Et_2O. . Isolated as a single diastereoisomer as an orange solid (157 mg, 54%): mp 141−143 °C; R_f 0.16 (15% acetone/petroleum ether); IR ν_{max} (thin film) 3063, 2968, 2936, 1551, 1509, 1345, cm^{-1}; ^1H NMR δ 0.73 (3H, t, *J* = 7.3), 1.73 (1H, ddq, *J* = 13.8, 7.3, 3.8), 1.81 (1H, dqd, *J* = 13.8, 11.4, 7.3), 3.67 (3H, s), 3.78 (1H, td, *J* = 11.1, 3.7), 4.14 (1H, dd, *J* = 10.8, 4.0), 5.04 (1H, d, *J* = 10.9), 6.27 (2H, m), 6.43 (2H, m), 7.06 (2H, m), 7.02−7.27 (3H, m), 7.43 (2H, m), 8.18 (2H, m); ^{13}C NMR δ 11.2 (CH_3), 24.7 (CH_2), 47.6 (CH), 55.2 (CH_3), 57.0 (CH), 97.6 (CH), 114.4 (2 CH), 114.5 (2 CH), 123.9 (2 CH), 125.7 (2 CH), 128.0 (CH), 128.7 (2 CH), 129.1 (2 CH), 137.0 (*C*), 139.1 (*C*), 145.5 (*C*), 147.2 (*C*), 152.3 (*C*); *m*/*z* (CI^+) 435 (M^+, 29); HRMS $C_{24}H_{25}N_3O_5$ calcd 435.17887, found 435.17926.

9*: No Ligand, Diethylzinc Addition, and Nitro-Mannich in THF, Protection with TFAA* . Analysis of the crude mixture after the nitro-Mannich step showed the ratio of diastereoisomers to be 80:10:10:0. Analysis of the crude mixture after the protection step showed the ratio of diastereoisomers to be 100:0:0:0. Isolated as a single diastereoisomer as bright orange feathers (95 mg, 29%): mp 163 °C; R_f 0.22 (10% EtOAc/petroleum ether); IR ν_{max} (thin film) 3695, 2935, 1656, 1602, 1551, 1152 cm^{-1}; ^1H NMR δ 0.62 (2H, t, *J* = 7.3), 1.00−1.29 (6H, m), 1.53−1.77 (6H, m), 1.93 (1H, m), 3.17, (1H, td, *J* = 10.2, 4.1), 3.80 (3H, s), 3.93 (1H, ddd, *J* = 10.4, 8.3, 4.7), 5.09 (1H, dd, *J* = 9.7, 4.7), 6.84 (1H, d, *J* = 9.7),7.14−7.19 (3H, m), 7.27−7.33 (4H, m), 9.39 (1H, d, *J* = 10.2); ^{13}C NMR δ 11.6 (CH_3), 24.9 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 29.6 (CH_2), 30.8 (CH_2), 41.9 (CH), 48.5 (CH), 55.8 (CH_3), 56.7 (CH), 92.8 (CH), 110.2 (*C*), 112.7 (CH), 113.6 (CH), 117.4 (q, *J* = 292.0, CF_3), 127.8 (CH) 127.9 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 138.0 (*C*), 149.0 (*C*), 149.5 (*C*), 180.0 (q, *J* = 33.0, *C*═O); 19F (CDCl3, 376 MHz) δ −68.9 (3F, s, *CF*3); *m*/*z* (ESI^+) 493 (MH^+, 44) 515 (MNa^+, 9); HRMS $C_{26}H_{32}F_3N_2O_4$ calcd 493.2314, found 493.2303.

11*: No Ligand, Diethylzinc Addition, and Nitro-Mannich in* Et_2O. A solution of 3-buten-1-yl acetate (306 mg, 5.36 mmol) in pentane (1 mL) was added to Et_2BH (5.40 mL, 5.40 mmol, 1 M in hexanes) at 0 °C and the reaction stirred for 4 h. [Et_2BH was prepared by vigorously stirring Et_3B (30 mL, 30 mmol, 1 M in hexanes) and $BH_3 \cdot Me_2S$ (1.44 mL, 15.0 mmol) at 0 °C in a flask equipped with a bleed needle. Et_2BH can be stored at −37 °C for >1 month without degradation.] Volatile components of the reaction were then removed in vacuo to leave a pale brown oil, ^1H NMR analysis confirmed the absence of alkene protons. The reaction flask was purged with Ar and cooled to 0 °C. Et_2Zn (2.68 mL, 2.68 mmol) was added and the reaction returned to rt over 1 h. The reaction was then cooled to 0 °C and stirred under reduced pressure (1−2 mmHg) for 4 h. The pale brown residue was dissolved in hexanes (2 mL) and added to a mixture of *β*-nitrostyrene (100 mg, 0.671 mmol) and $Cu(OTf)_2$ (12 mg, 0.030 mmol) in Et_2O (2 mL) at −78 °C. The reaction was warmed to room temperature and stirred until complete by tlc analysis (approximately 20 h) and then cooled to −78 °C. A solution of imine (2 mmol) in dry Et_2O (2 mL) was added and the mixture stirred for 20 min. A solution of TFA (0.17 mL, 3.5 mmol) in Et_2O (0.2 mL) was added dropwise over 20 s and the reaction stirred for 2 h. The reaction was warmed to room temperature over 1 h to provide a suspension of white solid and vivid yellow supernatant. The reaction was quenched by the addition of Et_2O and saturated aq $NaHCO_3$. The layers were separated and the aqueous phase extracted with Et_2O. The

organic layers were combined and the solvent removed in vacuo to provide crude **11** as a brown oil. Purification by column chromatography (10% Me_2CO/Hexane) afforded pure **11** (184 mg, 58%) as a pale yellow solid: mp 111−113 °C; R_f 0.31 (10% Me_2CO/hexane); IR ν_{max} (thin film) 3412, 1703, 1552 cm^{-1}; ^1H NMR δ 1.15 (2H, m), 1.55 (3H, m), 1.83 (1H, m), 1.98 (3H, s), 3.68 (3H, s), 3.72 (1H, apt td, J = 11.2, 3.2), 3.94 (2H, m), 4.20 (1H, d, J = 10.4, 3.6), 4.93 (1H, dd, J = 11.2, 3.6), 5.06 (1H, d, J = 10.4), 6.28 (2H, m), 6.63 (2H, m), 7.06 (2H, m), 7.23 (5H, m), 7.33 (3H, m); ^{13}C NMR δ 20.9 (CH_3), 23.5 (CH_2), 28.2 (CH_2), 31.5 (CH_2), 46.2 (CH), 55.6 (CH_3), 57.0 (CH), 64.0 (CH_2), 98.9 (CH), 114.7 (2 × CH), 114.7 (2 × CH), 126.1 (2 × CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.9 (2 × CH), 129.2 (2 × CH), 138.0 (C), 138.1 (C), 139.9 (C), 152.3 (CH), 171.1 (C); m/z (EI^+) 477 (100, MH^+); HRMS $C_{28}H_{33}N_2O_5$ calcd 477.2384, found 477.2363.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, elucidation of relative and absolute stereochemistry, structures, and X-ray representations. This material is available free of charge via the Internet at http://pubs.acs.org.

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