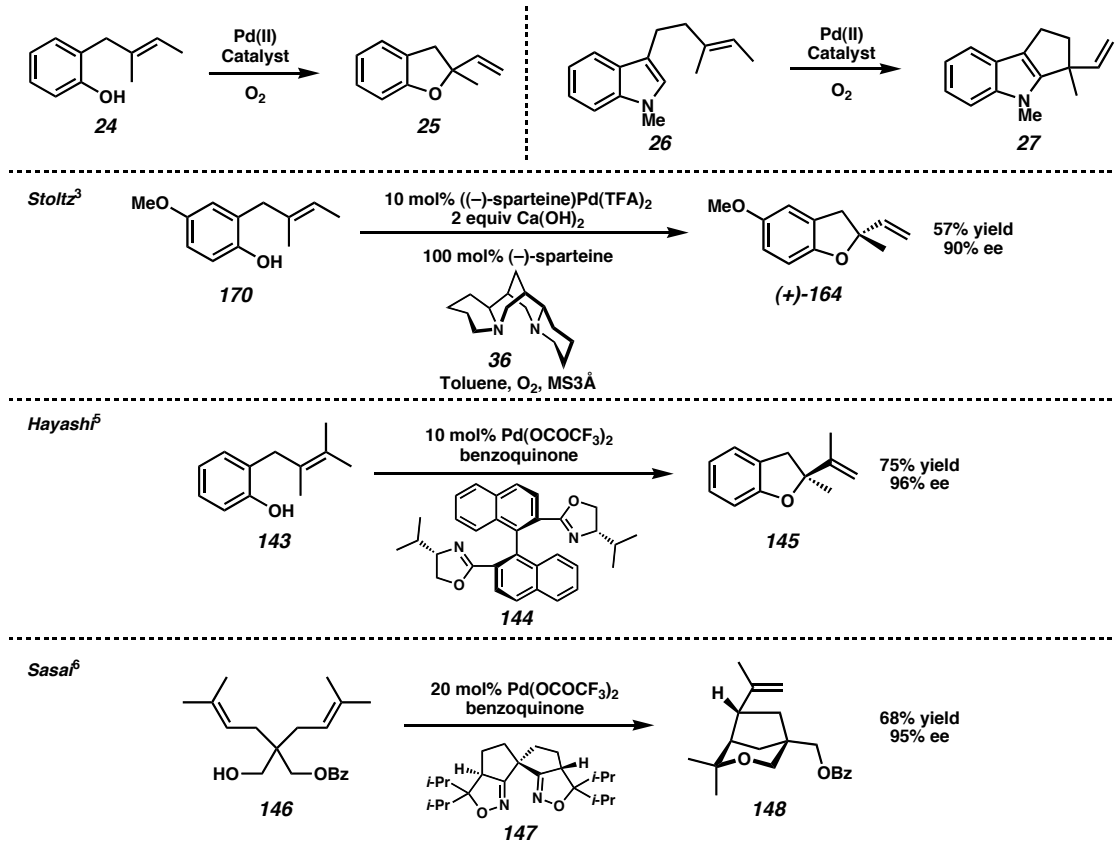
CHAPTER FIVE

Further Investigations into Palladium(II)-Catalyzed Asymmetric Oxidative Heterocyclizations

5.1 Introduction

Although significant progress had been made in a number of directions, the palladium(II) oxidation chemistry we had been investigating was at a crossroads (Scheme 5.1.1). The palladium/pyridine/O_2 system discovered by Uemura[1] for the oxidation of alcohols was used as a platform to develop the oxidative kinetic resolution of secondary alcohols.[2] Further investigations of the palladium/pyridine/O_2 system eventually led to the development of efficient cyclization reactions to form both heterocycles and carbocycles.[3,4] Importantly, one of these cyclization systems could be extended to a highly asymmetric variant by switching from pyridine to the chiral ligand (–)-sparteine. Although sparteine was effective for this isolated case, there was a significant lack of generality across a number of substrates. Moreover, the work by Hayashi[5] and Sasai[6] represent the only other cases where highly asymmetric heterocyclizations were realized. An important direction for this chemistry, therefore, is the development of asymmetric catalytic systems that can selectively cyclize new types of substrates. Described herein are our initial investigations of novel asymmetric oxidative heterocyclizations with chiral palladium(II) complexes.

Scheme 5.1.1



5.2 Heterocyclizations of Carboxylic Acids

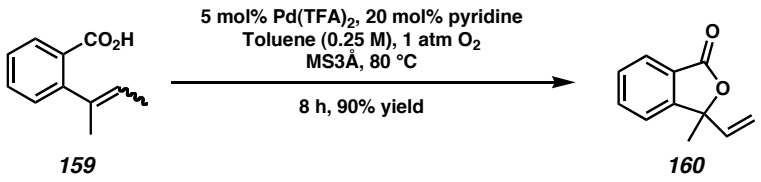
The first new substrate class that we chose to investigate for the heterocyclization chemistry was carboxylic acids. Based on our previous findings[3] and those of others,[7] it was well established that carboxylic acids with tethered olefin moieties will cyclize to lactones under palladium(II) oxidative conditions. We anticipated that the palladium/pyridine catalyst system could again be used as a platform to develop enantioselective variants. Moreover, there are few examples of enantioselective lactonization reactions deriving from the cyclization of carboxylic acids onto olefins, and of those reported, all exhibit modest selectivity.[8] Lactones are prevalent in countless

important bioactive molecules; the development of an efficient enantioselective lactonization would be highly useful for the synthetic community.

As a starting point, we decided to use catalysts possessing oxazoline ligands instead of sparteine-based derivatives. This decision was based both on the synthetic ease and availability of the oxazoline moiety (arising directly from chiral amino acids) and on its modular nature (allowing for straightforward variability). Both of these features were considerable advantages over the sparteine system we had previously investigated.

We first examined the cyclization of benzoic acid **159**. We had previously shown that under the standard $Pd(TFA)_2$/pyridine/O_2 conditions, **159** cyclized efficiently to lactone **160** (Scheme 5.2.1).[3] It should be noted that at the onset of this project, we hypothesized that it was important to use substrates as pure olefin isomers. It was anticipated that enantioselectivity would arise from face-selective binding of the olefin to the catalytic complex. Mixtures of olefin isomers would complicate the system because geometrical isomers have the potential to behave very differently in the reaction.

Scheme 5.2.1

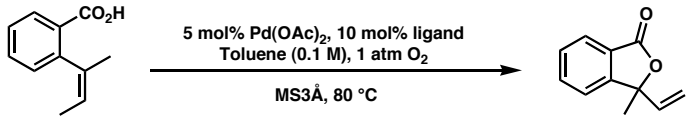


159 ***160***

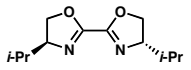
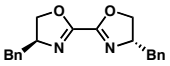
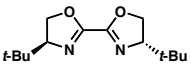
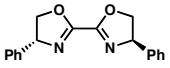
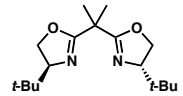
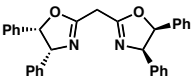
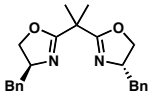
The $Pd(TFA)_2$/pyridine catalyst was substituted for $Pd(OAc)_2$/oxazoline catalysts in the cyclization of carboxylic acid **(*Z*)-159**, and the results of this preliminary screen are listed in Table 5.2.1. In general, oxazoline ligands did not suppress the reaction, and the cyclizations proceeded in the same timeframe as the pyridine systems. Enantioinduction

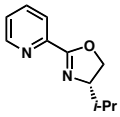
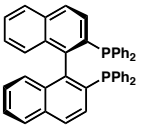
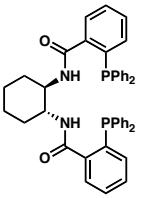
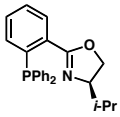
by the chiral ligands, however, was quite poor. Only in the case of ligand **393** (entry 3) did the ee exceed 10%. Ligands with phosphine moieties completely suppressed the oxidative cyclization to **160** (entries 9-11). Though the ee values were very low, these results still supported our hope that enantioinduction could occur in these reaction manifolds.

Table 5.2.1 Ligand screen for the oxidative cyclization of **(*Z*)-159**.



(Z)-159 *160*

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		*391*	5 h	73	7
			16 h	>95	8
2		*392*	5 h	75	0
			16 h	>95	0
3		*393*	5 h	65	12
			22 h	>95	11
4		*394*	5 h	30	4
			26 h	31	--[c]
5		*69*	5 h	55	0
			20 h	>95	0
6		*395*	20 h	>95	0
7		*396*	24 h	NR	--

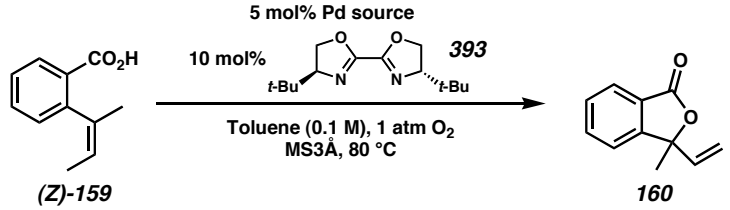
Entry	Ligand		time	Conv (%)[a]	% ee[b]
8		*397*	5 h	39	2
			20 h	>95	2
9		*56*	24 h	NR	--
10		*60*	24 h	NR	--
11		*398*	24 h	NR	--

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC. [c] % ee not measured.

We had observed significant effects on both reactivity and enantioselectivity depending on the palladium source during our previous studies on asymmetric palladium(II) reactions.[2a,3] We therefore examined the effect of the palladium source on the cyclization of carboxylic acid **(*Z*)-159** (Table 5.2.2). Although switching to $Pd(TFA)_2$ proved to be remarkably effective in our previous heterocyclization studies, it

did not prove fruitful here (entry 2). Reactivity was increased somewhat, but enantioselectivity was eroded. Chloride-based palladium precursors were much less reactive than $Pd(OAc)_2$ (entries 3 and 4). Following this initial screen, it appeared that $Pd(OAc)_2$ was the most effective palladium source for these cyclizations.[9]

Table 5.2.2 Palladium source screen for the oxidative cyclization of **(*Z*)-159**.

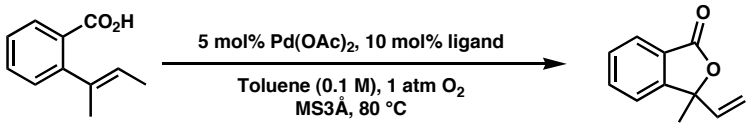


Entry	Pd source	time	Conv (%)[a]	% ee[b]
1	$Pd(OAc)_2$	5 h	65	12
		22 h	>95	11
2	$Pd(TFA)_2$	5 h	>90	6
3	$Pd(CH_3CN)_2Cl_2$	24 h	9	5
4	$Pd(nbd)Cl_2$	24 h	NR	--

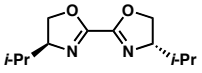
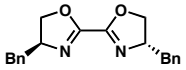
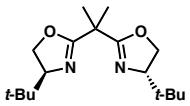
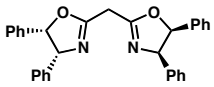
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC.

As mentioned above, we anticipated it was important to examine both olefin isomers of a cyclization substrate. Carboxylic acid **(*E*)-159** was thus subjected to Pd(II) cyclizations with several bisoxazoline ligands (Table 5.2.3). Again, the enantioselectivity in these reactions was found to be quite poor. The reactivity of this substrate was noticeably lower than the (*Z*)-olefin counterpart (compare to Table 5.2.1), confirming the notion that olefin geometry did indeed have an impact on the reactivity and would need to be considered in these studies.

Table 5.2.3 Ligand screen for the oxidative cyclization of **(*E*)-159**.



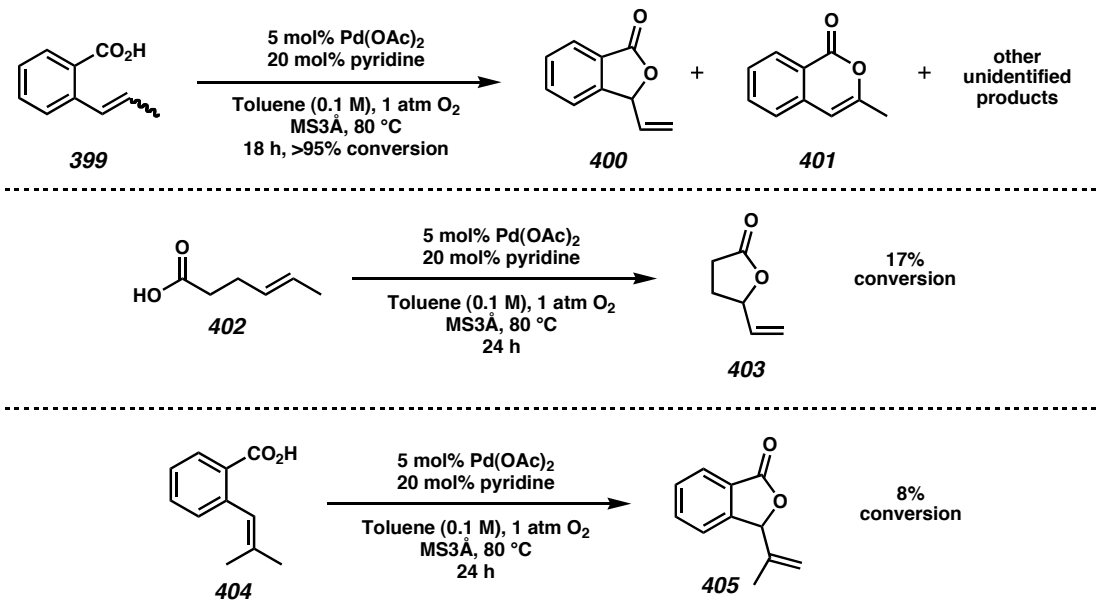
(E)-159 *160*

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		*391*	5 h	35	7
			20 h	54	6
2		*392*	5 h	43	2
			20 h	59	2
3		*69*	5 h	23	--[c]
			21 h	44	0
4		*395*	21 h	33	0

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC. [c] % ee not measured.

Other carboxylic acids (i.e., **399**, **402**, and **404**) were investigated in the early stages of experimentation. It was observed, however, that these acids had more complications than benzoic acids **(*Z*)-159** and **(*E*)-159**. Benzoic acid **399** did cyclize efficiently under the standard $Pd(OAc)_2$/pyridine conditions, but afforded multiple products arising from both exo and endo cyclization pathways (Scheme 5.2.2). Carboxylic acids **402** and **404** cyclized to lactones, but the reaction rates were quite sluggish compared to the other acids examined. Most of the substrates investigated have the alkene and the carboxyl group positioned on ortho substituents of a benzene ring. Carboxylic acid **402** may be relatively slow to react because it does not have the same conformational restrictions. It is not clear why carboxylic acid **404** was so unreactive; perhaps the olefin substitution pattern is simply not suited for this lactonization.

Scheme 5.2.2



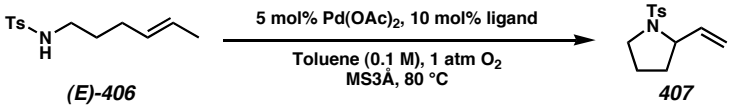
5.3 Heterocyclizations of Amines

5.3.1 Studies of the Cyclizations of Tosylamides

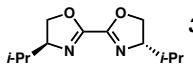
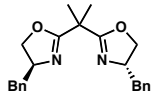
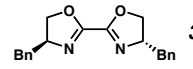
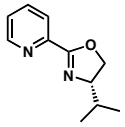
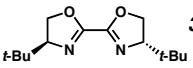
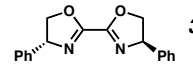
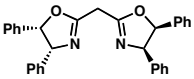
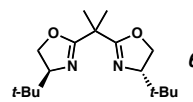
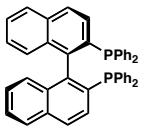
Although there were some promising leads in the lactonization reactions, both the low levels of enantioselectivity and the lack of substrate generality were discouraging. Consequently, we decided to investigate asymmetric intramolecular amination reactions. The palladium-catalyzed oxidative amination of olefins has been studied extensively.[10] Most relevant are reports by Larock ($Pd(OAc)_2$, DMSO, O_2)[11] and Stahl ($Pd(OAc)_2$, pyridine, O_2)[12] that have demonstrated that intramolecular cyclizations of tosylamides proceed efficiently under aerobic oxidative conditions. Both of these reports highlighted the importance of a *p*-toluenesulfonyl (tosyl) group on the nitrogen nucleophile. The tosyl group is electron-withdrawing, presumably preventing a nitrogen binding event that would preclude cyclization. We therefore began our studies of the intramolecular amination reactions by utilizing tosylamides as our substrates.

Tosylamide **(*E*)-406** was subjected to palladium(II) oxidative conditions with a variety of chiral ligands (Table 5.3.1).[13] As in the cases of the carboxylic acids, the bisoxazolines that are directly attached to each other through a single sigma bond (**391-394**, entries 1-4) were the most effective at enantioinduction (up to 23% ee). Pyridine-oxazoline **397** was promising as well (entry 7), providing moderate levels of reactivity with modest enantioselectivity (20% ee). Bisoxazolines with a bridging carbon were less effective ligands for this reaction, both in reactivity and selectivity (entries 5, 6, and 8). Though the levels of reactivity and selectivity in the tosylamide cyclizations were still lower than hoped, these cyclizations still represented a significant improvement over the aforementioned lactonization reactions.

Table 5.3.1 Ligand screen for the oxidative cyclization of **(*E*)-406**.



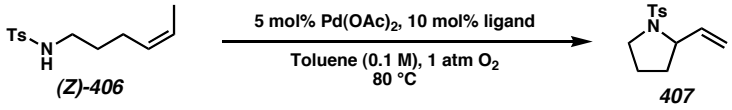
(E)-406 *407*

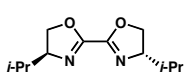
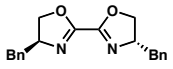
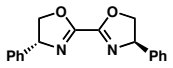
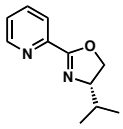
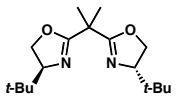
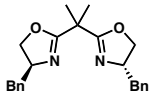
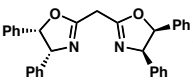
Entry	Ligand		time	Conv (%)[a]	% ee[b,c]	Entry	Ligand		time	Conv (%)[a]	% ee[b,c]
1		*391*	4 h 24 h	33 43	10 6	6		*396*	24 h	NR	--
2		*392*	4 h 24 h	10 25	23 20	7[d]		*397*	4 h 24 h	17 42	--[e] 20
3		*393*	4 h 24 h	15 20	10 8						
4[d]		*394*	5 h 24 h	<5 9	-12 -15	8[d]		*395*	24 h	NR	--
5		*69*	4 h 24 h	12 13	-3 3	9[d]		*56*	4 h 24 h	<5 7	-- --[e]

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured. [d] Reaction run without MS3Å. [e] % ee not measured.

We also examined the cis isomer of the tosylamide (**(*Z*)-406**) under various cyclization catalysts (Table 5.3.2). Again, the bisoxazolines deriving from oxalate (**391**, **392**, and **394**, entries 1-3) and the pyridine-oxazolines (**397** and **408**, entries 4 and 5) were somewhat effective ligands for these cyclizations, achieving moderate reactivity and modest enantioselectivity. Additionally, there were measurable differences in both reactivity and selectivity between the cis and trans isomers of the tosylamide (**(*E*)-406** and **(*Z*)-406**, Tables 5.3.1 and 5.3.2). In general, the (*Z*)-olefin cyclized more efficiently and selectively than the (*E*)-olefin, though there were exceptions, and the differences were not particularly large.

Table 5.3.2 Ligand screen for the oxidative cyclization of **(*Z*)-406**.



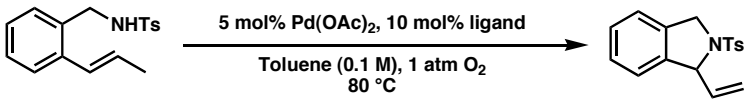
Entry	Ligand		time	Conv (%)[a]	% ee[b,c]
1		*391*	5 h 24 h	17 29	--[d] -7
2		*392*	5 h 24 h	32 44	--[d] 29
3		*394*	5 h 24 h	<5 <5	-- --
4		*397*	5 h 24 h	20 59	--[d] 36
5		*408*	5 h 24 h	12 40	--[d] 18
6		*69*	5 h 24 h	34 49	--[d] -2
7		*396*	24 h	NR	--
8		*395*	5 h 24 h	<5 38	-- -24

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured. [d] % ee not measured.

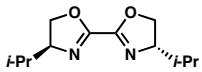
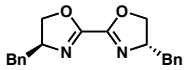
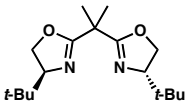
In an attempt to increase the reactivity of these systems, we investigated the cyclization of tosylamide **409**. By attaching the nucleophile and the olefin in an ortho

substitution pattern on a benzene ring, we hypothesized that the reactive partners would be forced into close proximity to each other and would therefore interact more readily. This proved to be true, as the oxidative cyclization of **409** proceeded more efficiently than the cyclization of tosylamide **406**. Tosylamide **409** was examined under a few catalyst systems (Table 5.3.3), all of which showed increased reactivity and selectivity compared to **406** under the same metal-ligand systems. Although this represented a promising lead for future work, the cyclizations of tosylanilines were even more selective (*vide infra*), and we consequently focused our attention on those substrates.

Table 5.3.3 Ligand screen for the oxidative cyclization of **409**.



409 ***410***

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		***391***	5 h 24 h	39 53	25 20
2		***392***	5 h 24 h	38 63	30 27
3		***69***	5 h	31	10

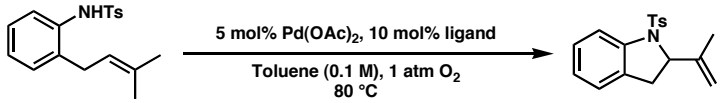
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

5.3.2 Studies of the Cyclizations of Tosylanilines and Derivatives

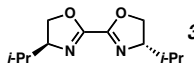
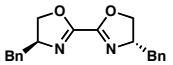
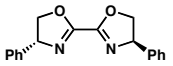
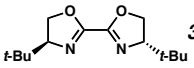
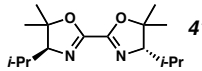
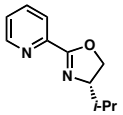
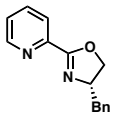
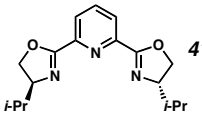
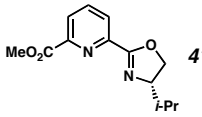
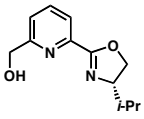
The asymmetric oxidative cyclization of tosylaniline **411** was investigated under a variety of palladium-ligand systems (Table 5.3.4). Although most of the ligands that were tested provided only marginal results, some interesting observations were made. Consistent with our previous results, bisoxazolines **391**-**393** and **413** were the most effective ligands with regard to reactivity and enantioselectivity (entries 1-5).

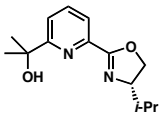
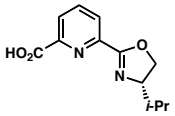
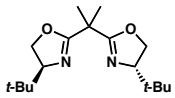
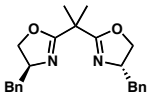
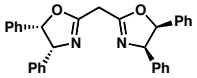
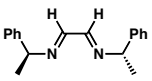
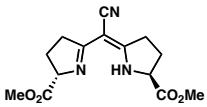
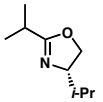
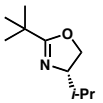
Bisoxazolines with larger backbones (entries 13-15, 20-25, and 36) afforded tosylindolines with much lower ee levels. Curiously, monooxazolines **421** and **422** hindered reactivity, in contrast to our findings with monodentate and bidentate pyridyl ligands (*vide infra*). Any ligand with an X-type donor (carboxylate, amide) completely shut down the cyclization reaction (entries 12, 17, and 32);[14] however, a tertiary alcohol moiety in the ligand framework caused a dramatic increase in the reactivity of the system (entries 11 and 27). This effect will be addressed in more detail later. Bisphosphine **56** (entry 33) and phosphoramidite **436** (entry 35) suppressed reactivity, suggesting that nitrogen-based ligands were more suited for this transformation than phosphorus-based ligands. Because valine-based bisoxazoline **391** provided the best combination of reactivity and selectivity (entry 1, 44% conversion and 34% ee after 24 h), it was utilized in further optimization studies.[15]

Table 5.3.4 Ligand screen for the oxidative cyclization of **411**.



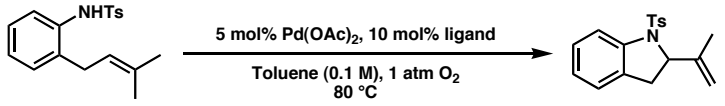
411 ***412***

Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
1	 ***391***	5 h 24 h	30 44	34 34
2	 ***392***	5 h 24 h	13 20	41 37
3	 ***394***	5 h 24 h	8 15	-24 -27
4	 ***393***	5 h 24 h	33 69	25 24
5	 ***413***	5 h 24 h	51 71	34 33
6	 ***397***	5 h 24 h	12 22	-12 -24
7	 ***408***	5 h 24 h	17 29	6 -2
8	 ***414***	5 h 24 h	9 21	21 18
9	 ***415***	5 h 24 h	<5 7	-- 27
10	 ***416***	5 h 24 h	<5 5	-- 37

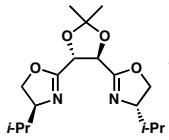
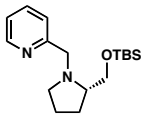
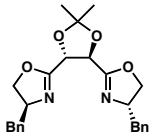
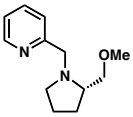
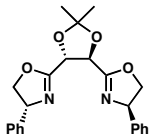
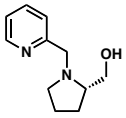
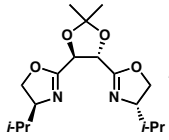
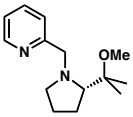
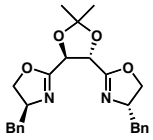
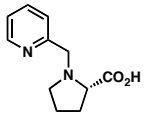
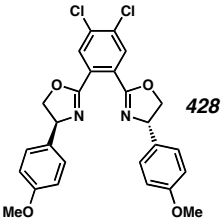
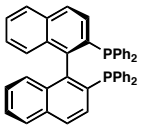
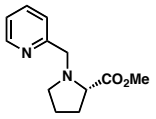
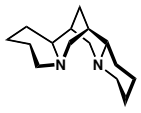
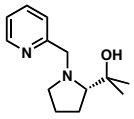
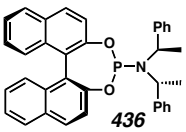
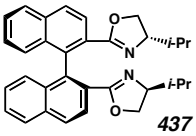
Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
11	 ***417***	5 h 24 h	35 77	24 24
12	 ***418***	24 h	NR	--
13	 ***69***	5 h 24 h	48 53	9 11
14	 ***396***	24 h	<5	--
15	 ***395***	24 h	NR	--
16	 ***419***	6 h	9	-3
17	 ***420***	24 h	NR	--
18[d]	 ***421***	5 h 24 h	NR <5	-- 4
19[d]	 ***422***	5 h 24 h	<5 8	-- -12

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. The sign corresponds to the sign of optical rotation, which was measured. [d] 20 mol% ligand.

Table 5.3.4 (continued)



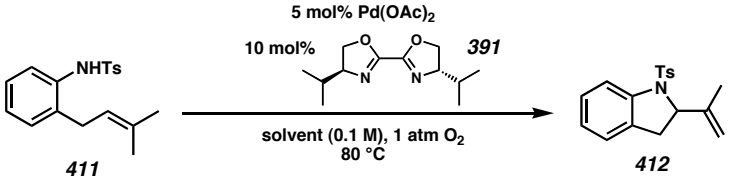
411 **→** ***412***

Entry	Ligand	time	Conv (%)[a]	% ee[b,c]	Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
20	 ***423***	6 h	20	2	28	 ***431***	5 h	18	-2
21	 ***424***	5 h	20	0	29	 ***432***	5 h	10	-4
22	 ***425***	5 h 48 h	29 65	-9 -9	30	 ***433***	5 h 24 h	66 79	8 9
23	 ***426***	5 h	26	7	31	 ***434***	5 h 24 h	26 31	-9 -9
24	 ***427***	5 h	36	6	32	 ***435***	24 h	NR	--
25	 ***428***	5 h 48 h	12 38	-8 -7	33	 ***56***	4 h 24 h	4 10	7 2
26	 ***429***	5 h 24 h 48 h	<5 12 16	16 25 25	34	 ***36***	5 h 24 h	<5 12	-12 -7
27	 ***430***	5 h 14 h	79 >95	-5 -4	35	 ***436***	5 h	<5	-2
					36	 ***437***	24 h	<5	--

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. The sign corresponds to the sign of optical rotation, which was measured.

Having found a promising ligand, we then investigated other parameters of the cyclization of tosylaniline **411**.[16] The solvent had a noticeable effect on the selectivity of the reaction (Table 5.3.5). Solvents with modest electron-donating capabilities (*t*-amyl alcohol, pinacolone) resulted in marginal decreases in reactivity and selectivity (entries 3 and 4). Solvents with stronger electron-donating moieties (DMF, CH_3CN) essentially shut down enantioselectivity (entries 7 and 8). In these instances, the solvent is most likely binding to the metal center, perhaps completely displacing the bisoxazoline ligand. The effects of various solvents seemed to imply that the bisoxazoline ligand was somewhat weakly bound to the metal center, potentially preventing high levels of enantioinduction in the cyclization reaction. Toluene, lacking any coordinative moieties, appeared to be the solvent of choice for this system and was used in subsequent optimization.

Table 5.3.5 Solvent screen for the oxidative cyclization of **411**.

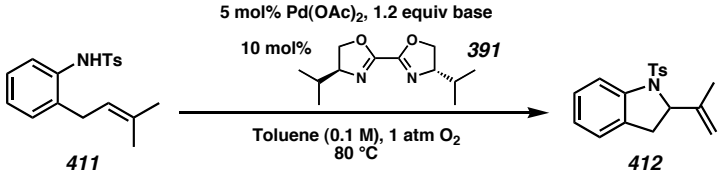


Entry	Solvent	time	Conv (%)[a]	% ee[b]
1	toluene	5 h	30	34
		24 h	44	34
2	DCE	5 h	5	18
		24 h	7	18
3	*t*-amyl alcohol	5 h	23	24
		29 h	34	26
4	pinacolone	5 h	15	20
		24 h	17	20
5	chlorobenzene	5 h	21	27
		24 h	25	25
6	dioxane	5 h	c	--
7	DMF	5 h	44	4
8	CH_3CN	5 h	12	1

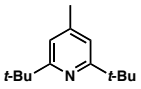
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] Substantial decomposition was observed.

The effect of a base additive was also examined in the oxidative cyclization of **411** (Table 5.3.6). It was hypothesized that an exogenous base could partially deprotonate the tosylaniline, increasing its nucleophilicity and thus the overall reactivity. Some bases did in fact increase the level of reactivity, but only marginally. LiOAc provided the largest improvement over the base-free conditions (entry 2 vs. entry 1). Some bases resulted in a dramatic erosion in enantioselectivity (entries 7, 8, and 14); it is not clear whether this erosion stems from a change in catalyst activity or an epimerization of product tosylindoline **412**. Stronger bases simply resulted in heavy decomposition (entries 11-13 and 15). Because the improvements caused by mild base additives were essentially insignificant, bases were not used in further optimizations.

Table 5.3.6 Base additives in the oxidative cyclization of **411**.



411 412

Entry	Base	time	Conv (%)[a]	% ee[b]	Entry	Base	time	Conv (%)[a]	% ee[b]
1	none	5 h	30	34	10	$KHCO_3$	5 h	42	30
		24 h	44	34			24 h	58	25
2	LiOAc	5 h	33	37	11	NaO*t*-Bu	5 h	d	--
		24 h	54	38					
3	NaOAc	5 h	35	36	12	KO*t*-Bu	5 h	d	--
		24 h	59	37					
4	KOAc	5 h	37	32	13	KHMDS	5 h	d	--
		24 h	57	31					
5	Li_2CO_3	5 h	35	33	14	$LiOH{\cdot}H_2O$	5 h	30	0
		24 h	51	35					
6	Na_2CO_3	5 h	29	32	15	NaOH	5 h	d	--
		24 h	49	31					
7	K_2CO_3	5 h	34	0	16	$Ca(OH)_2$	5 h	35	33
		24 h	67	0			24 h	54	34
8[c]	Cs_2CO_3	5 h	12	8	17[c]		5 h	32	37
		24 h	20	12			24 h	44	35
9	$NaHCO_3$	5 h	30	34					
		24 h	50	34					

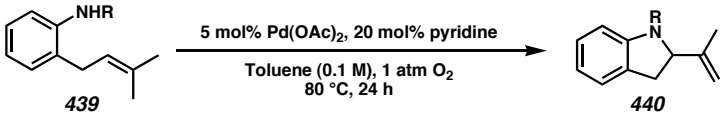
438

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] 2 equiv base were used. [d] Substantial decomposition was observed.

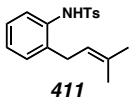
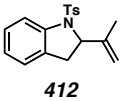
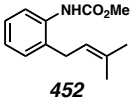
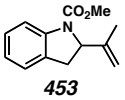
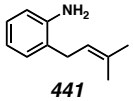
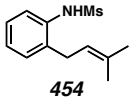
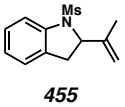
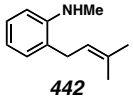
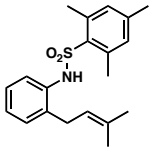
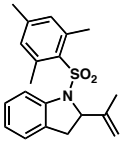
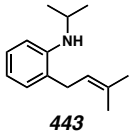
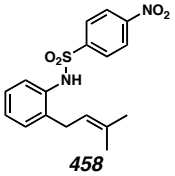
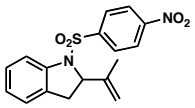
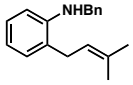
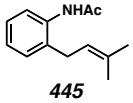
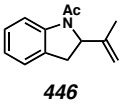
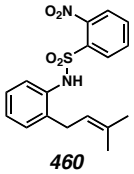
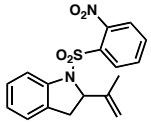
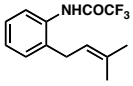
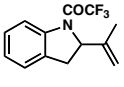
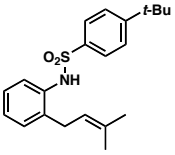
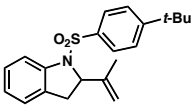
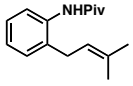
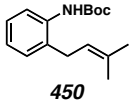
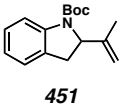
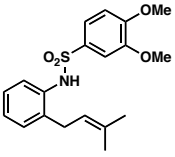
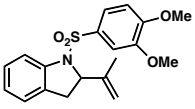
Substrate variations of tosylaniline **411** were investigated next. The *p*-toluenesulfonyl group was substituted by a variety of functional groups. These anilines were then cyclized under the standard palladium/pyridine conditions (Table 5.3.7). Some general trends were observed. Both free aniline (entry 2) and alkyl-substituted anilines (entries 3-5) were completely unreactive to oxidative cyclization. This could be because the nitrogen is now electron-rich enough to act as a ligand to the metal center. Another possibility is that the pK_a of the amine nitrogen is too high in the alkyl anilines to undergo deprotonation.[17] Amide functionalities could act as nucleophiles for the cyclization (entries 6-8), although the reactivities were noticeably lower. Carbamates were

comparable in reactivity to the parent sulfonamide (entries 9 and 10), and other sulfonamides also demonstrated comparable reactivity (entries 11-16). The only exceptions were arylsulfonamides with ortho substituents (entries 12 and 14), which appeared to hinder cyclization. This was somewhat surprising, as it was anticipated that the sterics were far enough removed from the nucleophilic center that they would not interfere with the cyclization.

Table 5.3.7 Examination of different aniline substituents in racemic cyclizations.



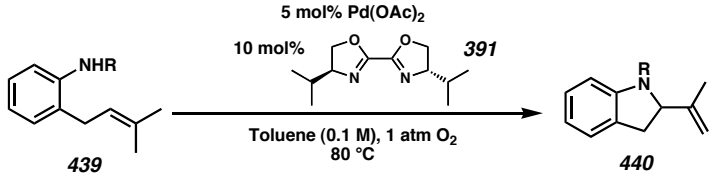
439 440

Entry	Substrate	Product	Conv (%)[a]	Entry	Substrate	Product	Conv (%)[a]
1	 411	 412	69	10	 452	 453	69
2	 441		NR	11	 454	 455	71
3	 442		NR	12	 456	 457	19
4	 443		NR	13	 458	 459	70
5	 444		NR[b]				
6	 445	 446	50	14	 460	 461	10
7	 447	 448	10	15	 462	 463	>95
8	 449		NR				
9	 450	 451	85	16	 464	 465	79

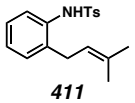
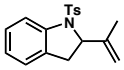
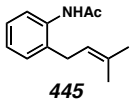
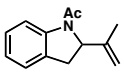
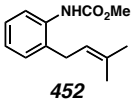
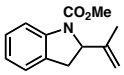
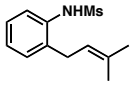
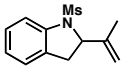
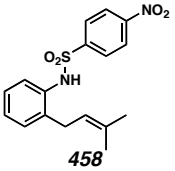
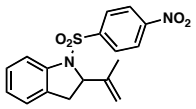
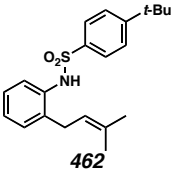
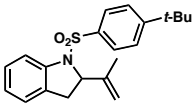
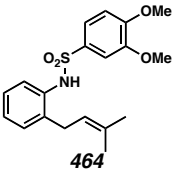
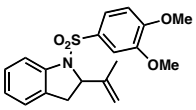
[a] % conversion measured by ^{1}H NMR. [b] Oxidation to the imine was observed.

The substrates that were effective in the racemic cyclization were then investigated under our best asymmetric cyclization conditions (Table 5.3.8). Both acetanilide **445** and methyl carbamate **452** were unreactive under these conditions (entries 2 and 3), and amides and carbamates were not explored further. Other sulfonamides were similarly reactive to tosylaniline **411** (entries 4-7). The enantioselectivities were also about the same as that of tosylaniline **411**, with the exception of the marginally lower *p*-nitrobenzenesulfonamide (**458**). It appeared from these experiments that altering the substituent on the nitrogen was not a good strategy for optimization because interchanging sulfonamides caused little to no change, while replacing the sulfonamide with another type of substituent shut down the reactivity.

Table 5.3.8 Examination of different aniline substituents in asymmetric cyclizations.



439 440

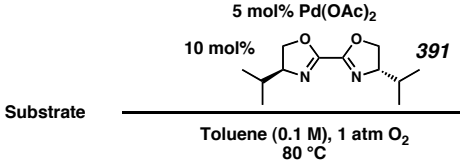
Entry	Substrate	Product	time	Conv (%)[a]	% ee[b]
1	 411	 412	5 h 24 h	42 56	34 34
2	 445	 446	24 h	<5	7
3	 452	 453	24 h	<5	--
4	 454	 455	5 h 24 h	36 50	28 28
5	 458	 459	5 h 24 h	44 56	20 23
6	 462	 463	5 h 24 h	31 45	32 27
7	 464	 465	5 h 24 h	34 47	34 33

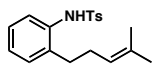
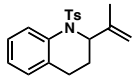
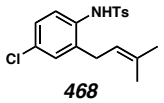
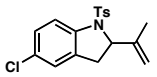
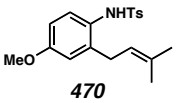
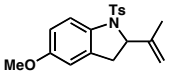
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

Other substrate variations were also met with no improvement (Table 5.3.9). The one carbon homolog of the original tosylaniline was less reactive and less selective. Aryl substitutions on the aniline ring also proved less effective. An electron-withdrawing group caused a decrease in reactivity (entry 2), likely due to the reduced nucleophilicity

of the nitrogen atom. The electron-donating methoxy group also had a negative effect, both on reactivity and selectivity. The origin of this effect is not clear, but it could arise from substrate ligation to the metal center via the oxygen atom or the more electron-rich nitrogen atom. Nonetheless, these variations were not investigated further.

Table 5.3.9 Examination of substrate variations in the asymmetric cyclization.



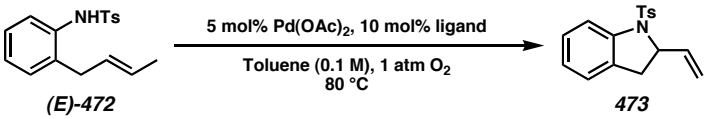
Entry	Substrate	Product	time	Conv (%)[a]	% ee[b]
1	 **466**	 **467**	24 h	17	11
2	 **468**	 **469**	5 h 24 h	14 19	36 33
3	 **470**	 **472**	5 h 24 h	21 30	26 18

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

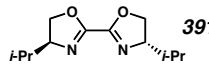
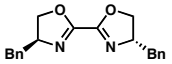
The final substrate variation that was investigated was the olefin substitution pattern. Specifically, trans and cis substituted olefins **(*E*)-472** and **(*Z*)-472** were subjected to asymmetric oxidative conditions (Tables 5.3.10 and 5.3.11). Both of these substrates cyclized significantly faster than the trisubstituted olefin. This is consistent with what has been found by Larock[11] and Stahl[12] in their tosylamide cyclization studies—a disubstituted olefin is generally more reactive because there are fewer steric interactions in the Pd(II) olefin activation event. The levels of enantioselectivity, however, were markedly lower in these cyclizations. These substrates were not

optimized further, but it is possible that conditions more favorable for enantioselective reactions (i.e., lower temperatures) could lead to improvements.[18]

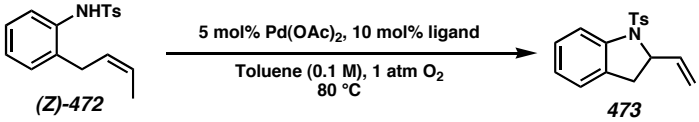
Tables 5.3.10 and 5.3.11 Oxidative cyclizations of disubstituted olefin substrates.



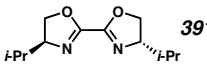
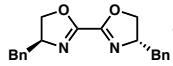
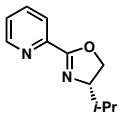
(E)-472 *473*

Entry	Ligand	time	Conv (%)[a]	% ee[b]
1	 *391*	5 h	>95	20
		10 h	>95	19
2	 *392*	5 h	>95	13
		24 h	>95	12

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.



(Z)-472 *473*

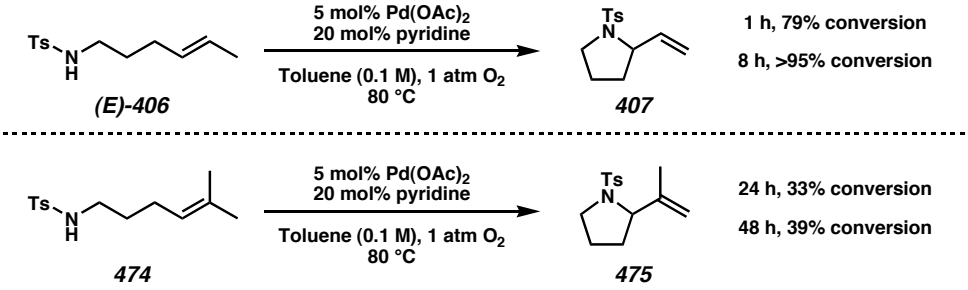
Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
1	 *391*	5 h	92	22
		24 h	>95	22
2	 *392*	5 h	80	6
		24 h	>95	6
3	 *397*	5 h	92	-16
		24 h	>95	-15

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured.

Regarding the alkene substitution pattern and its impact on overall reactivity, we also compared disubstituted olefin **(*E*)-406** and trisubstituted olefin **474** in the oxidative cyclization (Scheme 5.3.1). Under the standard $Pd(OAc)_2$/pyridine conditions, tosylamide **(*E*)-406** cyclized efficiently to pyrrolidine **407**. The trisubstituted olefin

(**474**), however, reacted much more sluggishly. This comparison further demonstrated the impact of alkene substitution on these Pd(II) catalyzed oxidative cyclizations.

Scheme 5.3.1



5.4 Probing the Mechanism

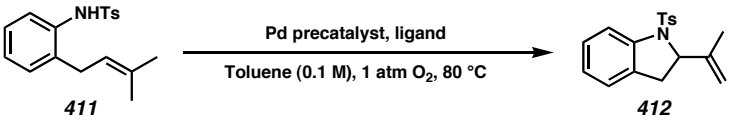
Although the screening of various ligand-substrate combinations had proven effective in finding initial leads, the overall improvement was modest. High enantioselectivities could not be realized under any of these systems, and reactivity was quite variable. It became clear that this screening process was limited in potential, and a firmer understanding of how the reaction was proceeding was needed. We therefore embarked on a more detailed study of this cyclization in hopes of rationalizing some of our observations to ultimately provide a stronger basis for further explorations.

5.4.1 Monodentate and Bidentate Ligand Effects

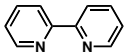
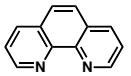
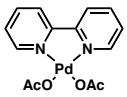
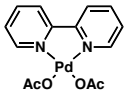
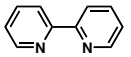
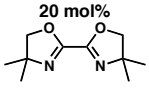
The first aspect of the oxidative cyclization we studied was the effect of monodentate versus bidentate ligands. In the racemic oxidative cyclizations studied by our group[3] and Stahl,[12] it was found that pyridine, a monodentate ligand, served as the optimal ligand. Bidentate ligands on metals are generally more effective at inducing asymmetry in enantioselective catalytic transformations because of the increased organization of the catalyst complex. Monodentate and bidentate variants of both

pyridine and oxazoline ligands were examined in the oxidative cyclization of tosylaniline **411** (Table 5.4.1). In the pyridine class, systems with monodentate ligands were clearly more reactive than bidentate ones (entry 1 vs. entries 2-5). Importantly, added bipyridine slowed down the reaction (compare entries 4 and 5). Stahl has found that in detailed mechanistic studies of the palladium(II)-catalyzed oxidation of alcohols, several catalytic intermediates only have one pyridine ligand bound to the metal center.[19] It could be that the second pyridyl moiety in the bidentate ligands is hindering the ability to access these intermediates, resulting in sluggish reactions.

Table 5.4.1 Monodentate and bidentate ligands in the cyclization of **411**.



411 ***412***

Entry	Pd precatalyst	Added Ligand	time	Conv (%)[a]
1	5 mol% $Pd(OAc)_2$	20 mol% pyridine	5 h	33
			24 h	69
			44 h	>95
2	5 mol% $Pd(OAc)_2$	10 mol%  ***476***	8 h	3
			24 h	9
3	5 mol% $Pd(OAc)_2$	10 mol%  ***477***	8 h	3
			24 h	8
4	5 mol%  ***478***	none	5 h	7
			24 h	17
5	5 mol%  ***478***	5 mol%  ***476***	5 h	2
			24 h	8
6	5 mol% $Pd(OAc)_2$	20 mol%  ***479***	5 h	<5
			24 h	12
7	10 mol% $Pd(OAc)_2$	20 mol%  ***480***	24 h	62

[a] % conversion measured by ^{1}H NMR.

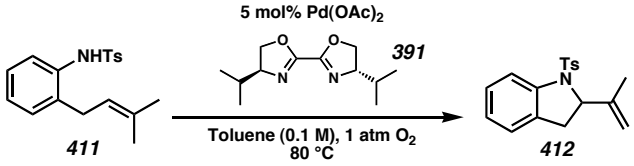
Surprisingly, the same monodentate-bidentate comparison did not extend to oxazolines (entries 6 and 7, Table 5.4.1). Monodentate oxazoline **479** hindered the reaction, whereas bisoxazoline **480** was a competent ligand for this reaction. The difference between these two ligands compared to the differences in the pyridine class is remarkable. It is currently unclear why this reversal occurs, but it could represent a change in mechanism. More detailed mechanistic studies would need to be conducted to explain this effect, but for the purposes of this study, it should be noted that bidentate ligands are not necessarily worse in catalyst design.

5.4.2 Ligand:Palladium Ratio Studies

We also investigated the effect of the ligand to palladium ratio in the oxidative cyclization of tosylaniline **411** (Table 5.4.2). There was a subtle increase in enantioselectivity in moving from 5 to 15 mol% ligand (entries 1-3). At 100 mol% ligand, the level of enantioselectivity was about the same as at 15 mol%, but the reactivity was significantly lower. A dynamic equilibrium between ligated and nonligated palladium centers is consistent with these observations (Scheme 5.4.1). At low ligand concentrations (5 mol%), an unselective background pathway involving nonligated palladium complexes **481** or **482** could be more prevalent and would account for the decreased enantioselectivity. At higher concentrations, this background reaction is suppressed. The low reactivity at 100 mol% ligand could be attributed to a second bisoxazoline competitively binding to the metal center (**484**), preventing catalysis. Another possible explanation is that the Pd-bisoxazoline complex **483**, heavily favored at

high ligand concentration, is exceptionally slow to react compared to free palladium catalysts **481** or **482**.[20]

Table 5.4.2 Examination of ligand **391** stoichiometry.

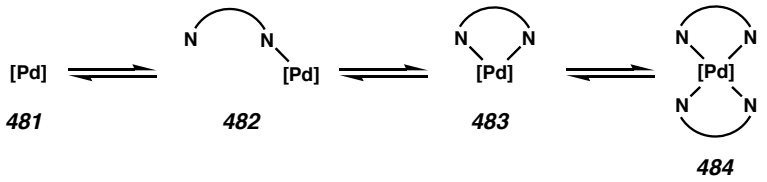


411 412

Entry	Ligand amt	time	Conv (%)[a]	% ee[b]
1	5 mol%	5 h	34	31
		24 h	46	29
2	10 mol%	5 h	42	34
		24 h	56	34
3	15 mol%	5 h	35	36
		24 h	50	36
4	100 mol%	5 h	16	37
		29 h	28	35

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

Scheme 5.4.1



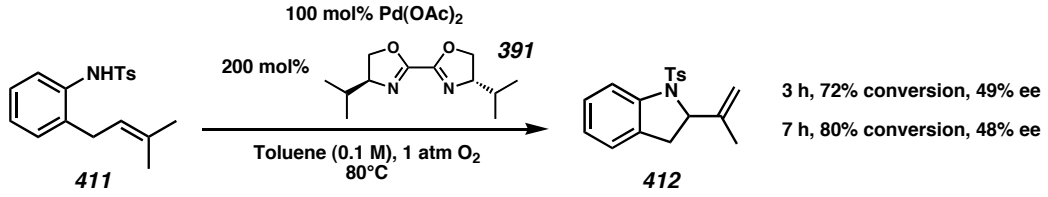
481 482 483 484

5.4.3 Stoichiometric Palladium Cyclizations

The oxidative cyclization of tosylaniline **411** was performed using a stoichiometric amount of the catalyst complex (Scheme 5.4.2). A significant increase in both conversion and enantioselectivity was observed. Conversion, albeit higher, seemed to stall after a short time. The enantioselectivity was also measurably higher than in the catalytic reactions. Both of these observations imply that the active, selective catalyst is not persisting in the reaction. Stahl has demonstrated that palladium catalysts can

undergo bimolecular decomposition by aggregation in Pd(II) oxidative reactions, which would be more likely at high catalyst concentration.[21] It is possible that this deactivation is occurring in this stoichiometric reaction (as well as in the catalytic reactions), which would help to explain the incomplete conversion.

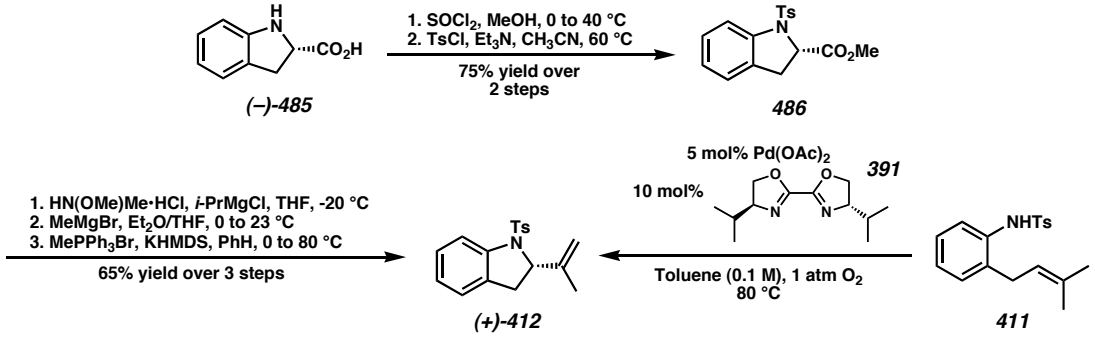
Scheme 5.4.2



5.4.4 Independent Synthesis of Tosylindoline 412

With a better understanding of the nature of the catalyst in these reactions, we hoped to investigate how the catalyst was interacting with the substrate in order to develop a clearer picture of the mode of enantioinduction. We first determined which enantiomer of tosylindoline **412** was preferentially being formed. This was accomplished via an independent synthesis (Scheme 5.4.3). Starting with (*S*)-indoline-2-carboxylic acid, methyl esterification and tosylation afforded indoline **486**. Indoline **486** was then converted to the Weinreb amide, which was treated with MeMgBr to afford the methyl ketone. Treatment with $MePPh_3Br$ provided enantiomerically pure tosylindoline **(+)-412**, which corresponds to the major enantiomer produced with the $Pd(OAc)_2$/bisoxazoline **391** catalyst.

Scheme 5.4.3

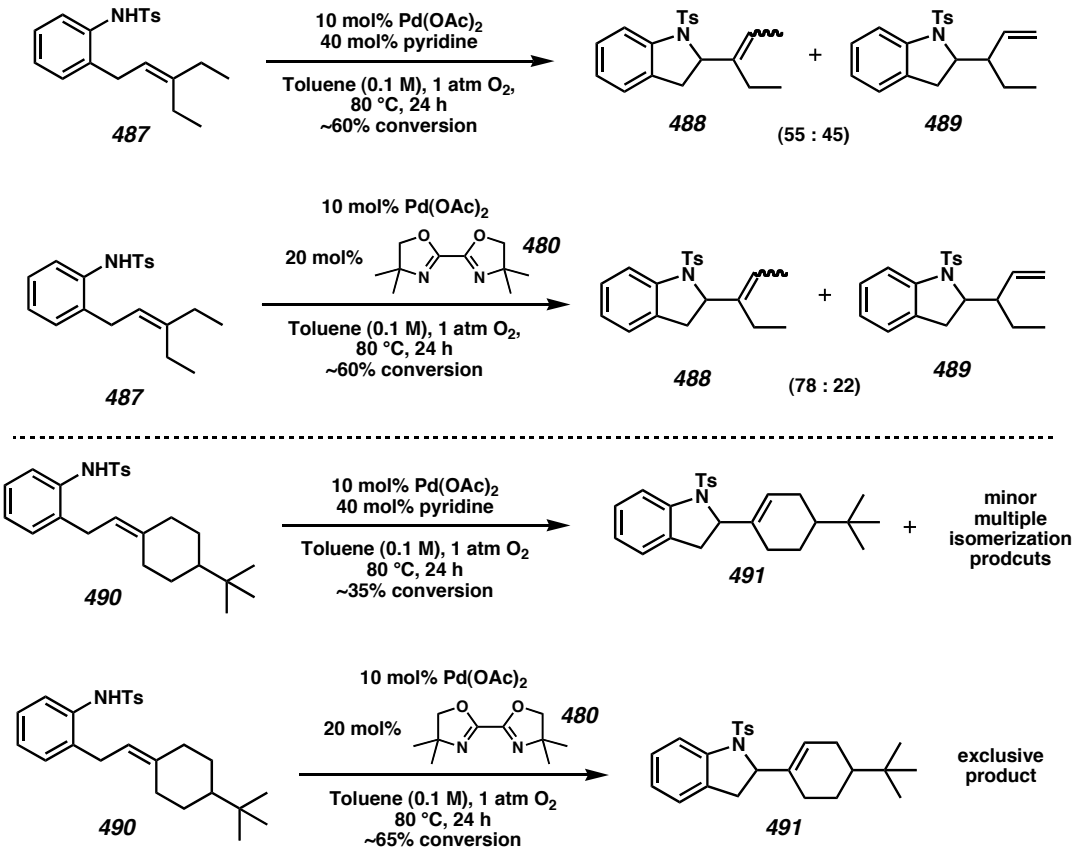


5.4.5 Palladium Hydride Mediated Olefin Isomerizations

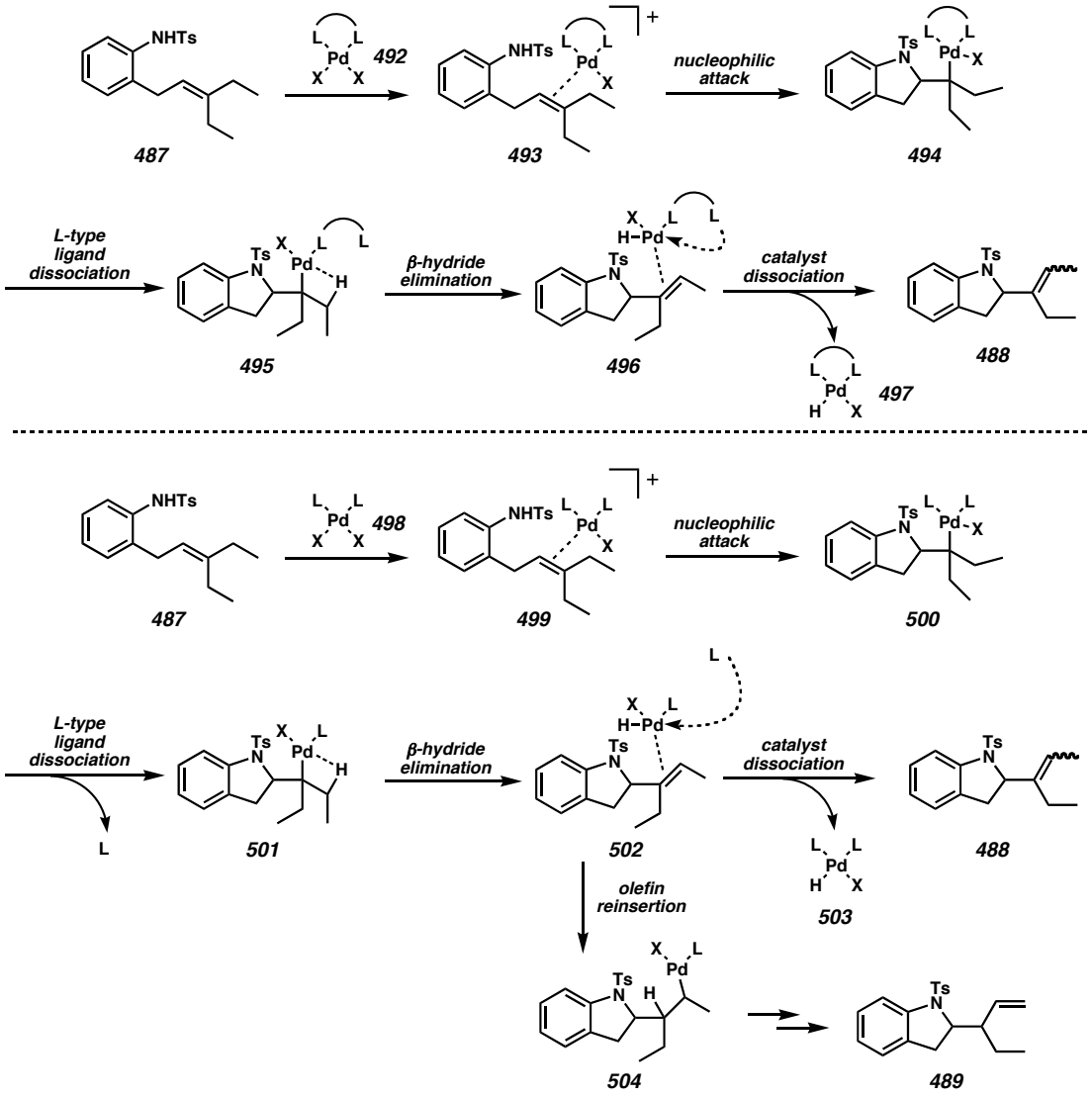
Palladium hydride intermediates, generated from the β-hydride elimination step, have been known to undergo olefin insertion reactions to form mixtures of olefin products. Olefin isomerization reactions were observed in some substrate tosylanilines (Scheme 5.4.4). Specifically, tosylaniline **487**, under the $Pd(OAc)_2$/pyridine conditions, afforded a mixture of tosylindolines **488** and **489**. **489** most likely arises from the palladium hydride reinsertion of the initial product olefin (**488**) and β-hydride elimination at the terminal methyl. The product distribution was different when bisoxazoline **480** was used as the ligand. In this case, palladium hydride reinsertion of the olefin was much less prevalent, and tosylindoline **488** was therefore the major isolated product. Olefin isomerizations also occurred in the oxidative cyclization of tosylaniline **490**. In this case, multiple isomerization products were observed in the $Pd(OAc)_2$/pyridine system, whereas no isomerizations were observed with the $Pd(OAc)_2$/bisoxazoline system. This result is consistent with the first example—palladium hydride mediated isomerizations occur more readily with monodentate pyridine ligands. The origin of this effect is unclear; one possible explanation is that L-type ligand dissociation must occur before β-hydride

elimination can happen (Scheme 5.4.5). Once the elimination occurs, the olefin ligand is readily displaced by the second coordinating atom of the bidentate ligand (intermediate **496**). In the pyridine case, this displacement must happen intermolecularly (intermediate **502**), which we expected to be slower than the intramolecular case. Therefore, olefin reinsertion to intermediate **504** would be more kinetically competitive, leading to increased levels of isomerization.

Scheme 5.4.4



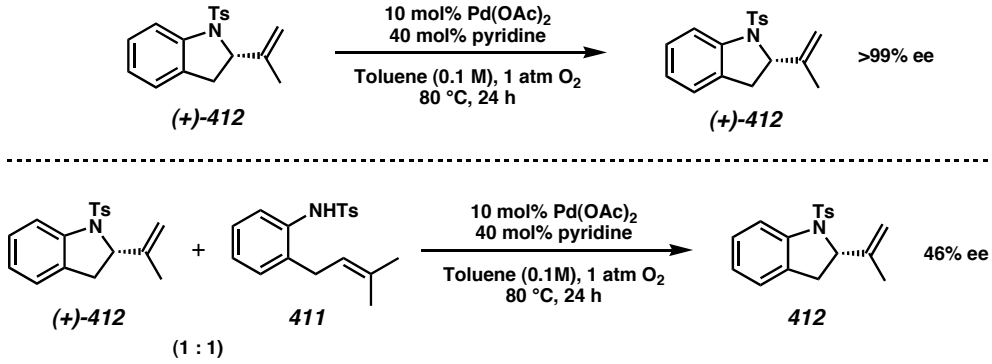
Scheme 5.4.5



To test whether palladium hydride species are detrimental to the overall enantioselectivity, enantiopure tosylindoline **(+)-412** was subjected to racemic reaction conditions (Scheme 5.4.6). After 24 h, the tosylindoline was reisolated without any evident racemization. The effect of intermediate palladium hydride species was also examined by subjecting a 1:1 mixture of enantiopure tosylindoline **(+)-412** and tosylaniline **411** to racemic cyclization conditions. The product tosylindoline was

isolated in 46% ee (73:27 er), within error of what was expected if palladium hydride species did not cause racemization in an intermolecular fashion. Once the palladium hydride dissociates from the product olefin, it proceeds to the catalyst reoxidation step rather than associate to a new olefin.

Scheme 5.4.6

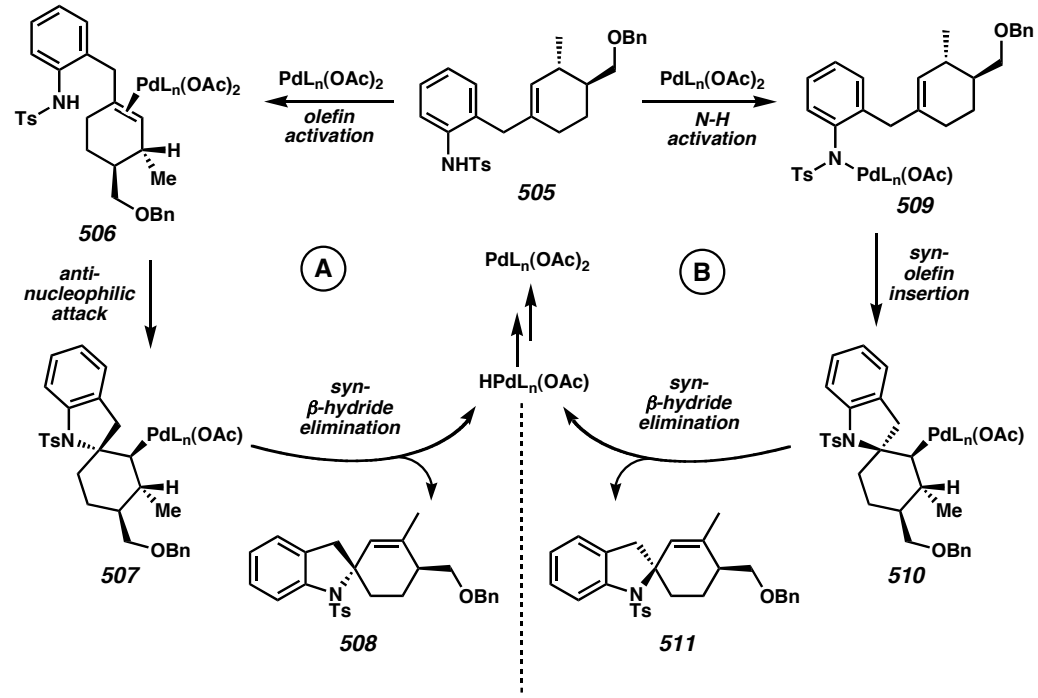


5.4.6 Distinguishing between a Wacker Mechanism and an Olefin Insertion Mechanism

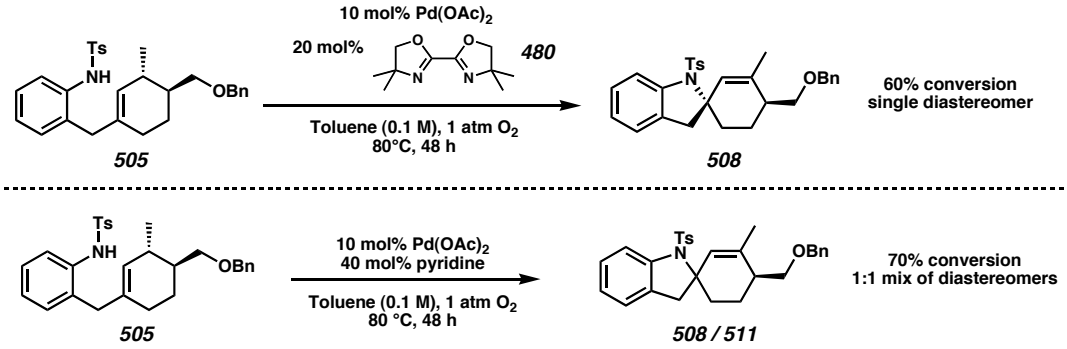
The final experiment conducted to provide insight into the asymmetric oxidation reaction was the cyclization of tosylaniline **505** (Scheme 5.4.7). As shown in our oxidative C-C bond forming chemistry, cyclization of this substrate can distinguish between two possible mechanistic pathways. Pathway A (Wacker-type mechanism) involves olefin activation, anti nucleophilic attack, and syn β-hydride elimination. Pathway B consists of an "N-H activation" step,[22] followed by a syn olefin insertion and a syn β-hydride elimination. When substrate **505** is subjected to the $Pd(OAc)_2$/bisoxazoline **480** catalyst system, tosylindoline **508** is isolated as a single diastereomer (Scheme 5.4.8). This outcome is consistent with a Wacker-type mechanism (pathway A). Interestingly, when substrate **505** is subjected to the $Pd(OAc)_2$/pyridine

system, both diastereomers were observed in an approximately 1:1 mixture. It remains unclear whether this mixture arises from both mechanisms being operative or palladium hydride mediated isomerizations of the initial product.[23]

Scheme 5.4.7



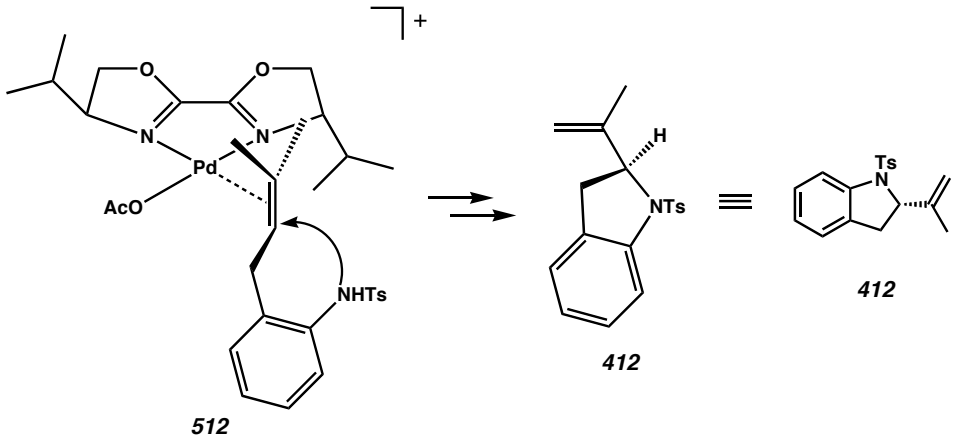
Scheme 5.4.8



5.4.7 A Proposed Stereochemical Model for the Observed Selectivity

Based on this outcome, a model describing the origin of enantioselectivity based on facially-selective olefin binding can be derived. It is believed that the alkene of tosylaniline **411** binds to the palladium center in the orientation depicted in Figure 5.4.1. The olefin binds to orient the proton of the less substituted carbon in the vicinity of the isopropyl group of the oxazoline. Anti selective nucleophilic attack on this bound olefin leads to the product with the stereocenter as drawn. This model is most consistent with the observed results[24] and could potentially be utilized in further ligand design.

Figure 5.4.1 Model for the observed selectivity in the asymmetric cyclization of **411**.



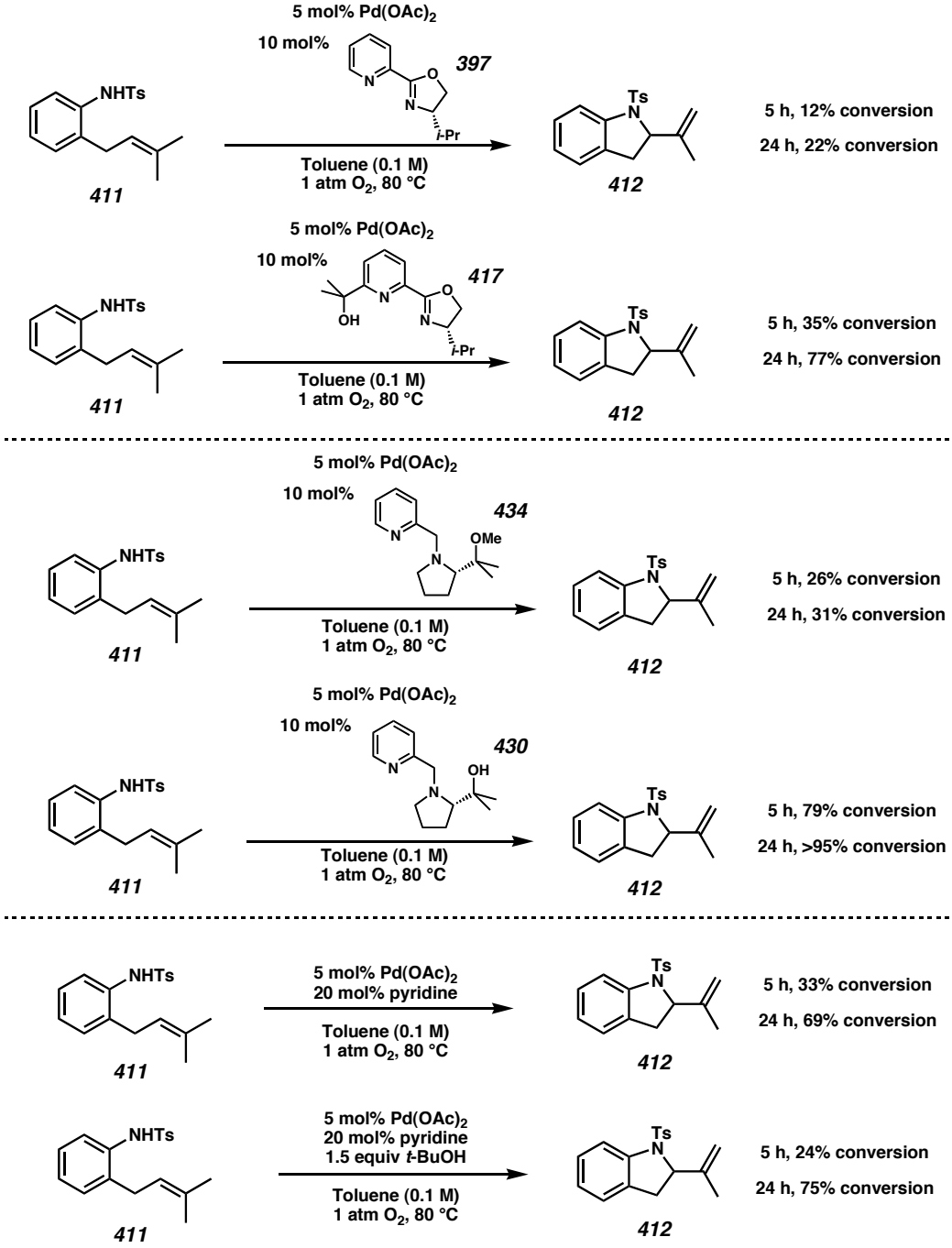
5.5 Further Developments

Although we have developed a reasonably clear picture of what is occurring in the oxidative cyclization of tosylaniline **411**, the levels of reactivity and enantioselectivity are not optimal. The largest obstacle in developing these reactions has been the effect of ligands on overall reactivity. Stahl has demonstrated that in palladium(II)-catalyzed alcohol oxidations, pyridine ligands accelerate the reoxidation of Pd(0), but decelerate the substrate oxidation.[19] The reactivity of Pd(II) centers toward substrate oxidation depends

highly on the electrophilicity of the metal center; bound ligands will increase the electron density of the metal center and thereby decrease its electrophilicity. Because of this ligand effect, the cyclizations typically need to be performed at high temperatures (i.e., 80 °C) for long periods of time, which are typically undesirable conditions for asymmetric transformations. Nonligated palladium centers, which would catalyze nonselective cyclizations, are expected to be more electrophilic (and consequently more reactive) than their ligated counterparts, further complicating the situation. Solutions to overcome these difficulties remain undiscovered.

A promising lead to this end is depicted in Scheme 5.5.1. During the ligand screening process of the cyclization of tosylaniline **411**, substantial increases in reactivity were observed when ligands possessing a tertiary alcohol were utilized (*vide supra*). Our previous studies on the palladium(II)-catalyzed oxidative kinetic resolution have demonstrated a dramatic rate effect caused by the presence of a tertiary alcohol in the reaction mixture.[2b] Direct comparisons of ligands **397** and **417** (with the tertiary alcohol moiety absent) and ligands **434** and **430** (with the tertiary alcohol replaced by a methyl ether) demonstrate the dramatic effects of this alcohol moiety. Importantly, when *t*-BuOH was added to the standard cyclization conditions, there was no noticeable effect on the rate, in contrast to our observations in the kinetic resolution chemistry. Though the origin of its effect remains to be elucidated, incorporation of a tertiary alcohol into the ligand framework could prove beneficial in the design of more reactive and selective systems.

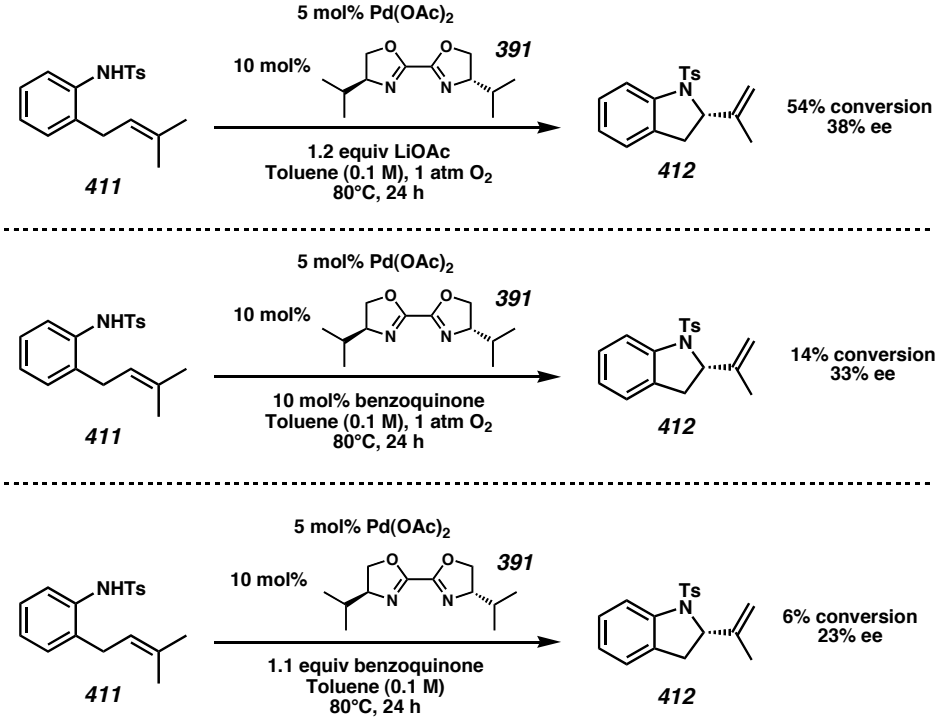
Scheme 5.5.1


5 mol% Pd(OAc)2
10 mol%
397
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
Ts
N
412
5 h, 12% conversion
24 h, 22% conversion
5 mol% Pd(OAc)2
10 mol%
417
OH
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 35% conversion
24 h, 77% conversion
5 mol% Pd(OAc)2
10 mol%
434
OMe
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 26% conversion
24 h, 31% conversion
5 mol% Pd(OAc)2
10 mol%
430
OH
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 79% conversion
24 h, >95% conversion
NHTs
411
5 mol% Pd(OAc)2
20 mol% pyridine
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 33% conversion
24 h, 69% conversion
NHTs
411
5 mol% Pd(OAc)2
20 mol% pyridine
1.5 equiv t-BuOH
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 24% conversion
24 h, 75% conversion

5.6 Conclusion

We have investigated further extensions into the palladium catalyzed asymmetric oxidative heterocyclization reactions. Although the levels of reactivity and enantioselectivity are modest at this point, our findings still represent the most selective examples of cyclizations of this type. A demonstration of the advantage of using the palladium/ligand/O_2 system is illustrated in Scheme 5.6.1. Under our best conditions to date, the cyclization of tosylaniline **411** proceeds in 54% conversion and 38% ee. Using the same system, but including 10 mol% benzoquinone as a cooxidant, both reactivity and selectivity drop measurably. When benzoquinone is used as the sole stoichiometric oxidant—currently the most utilized reoxidation system in asymmetric Pd(II) cyclization chemistry[5,6]—the levels of reactivity and selectivity are even lower. The palladium/ligand/O_2 system clearly provides an entry into new asymmetric oxidative transformations and holds promise for future developments.

Scheme 5.6.1


5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
1.2 equiv LiOAc
Toluene (0.1 M), 1 atm O2
80°C, 24 h
Ts
N
412
54% conversion
38% ee
5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
10 mol% benzoquinone
Toluene (0.1 M), 1 atm O2
80°C, 24 h
Ts
N
412
14% conversion
33% ee
5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
1.1 equiv benzoquinone
Toluene (0.1 M)
80°C, 24 h
Ts
N
412
6% conversion
23% ee

5.7 Experimental Section

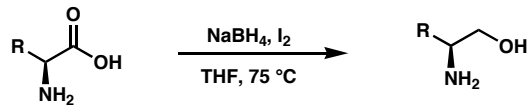
5.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received, except for benzoquinone, which was sublimed. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral GC was carried out using a Chiraldex B-DM column (30.0 m x 0.25 mm) purchased from Bodman Industries. Analytical chiral HPLC was performed on a Chiralcel AD or OD-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) or on a Varian Mercury 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C spectra were recorded on a Varian Mercury 300 (at 75 MHz) or on a Varian Mercury 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Unless otherwise noted, compounds that are mixtures of *E* and *Z* olefin isomers are reported as the mixture as seen by ^{1}H NMR. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

$Pd(nbd)Cl_2$ was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Lindlar's catalyst (5% palladium on $CaCO_3$ with lead poison) was purchased from Alfa Aesar, Ward Hill, MA. All other palladium salts were purchased from Strem Chemicals, Inc., Newburyport, MA. Ligands **56**, **60**, **398**, and **572** were purchased from Strem Chemicals, Inc., Newburyport, MA. Diimine **419** was acquired from Ryan McFadden in the Stoltz group. Phosphoramidite **436** was acquired from Douglas Behenna in the Stoltz group. Bisoxazoline **428** was acquired from Tehshik Yoon in the MacMillan group at the California Institute of Technology, Pasadena, CA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

5.7.2 Preparative Procedures

5.7.2.1 Synthesis of Ligands



R = i-Pr (513)
R = Bn (515)
R = t-Bu (517)

R = i-Pr (514)
R = Bn (516)
R = t-Bu (518)

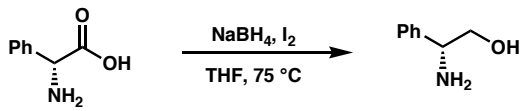
Synthesis of amino alcohols

L-Valinol. The reduction of amino acids was performed according to the procedure of McKennon et al.[25] To a suspension of $NaBH_4$ (6.20 g, 164 mmol) in 166 mL THF at 23 °C was added L-valine (8.00 g, 68.3 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (17.3 g, 68.3 mmol) in 41.4 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 125 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by distillation (35 °C/1 mm) to afford L-valinol[26] as a colorless oil.

L-Phenylalaninol. To a suspension of $NaBH_4$ (1.37 g, 36.2 mmol) in 36.2 mL THF at 23 °C was added L-phenylalanine (2.50 g, 15.1 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (3.83 g, 15.1 mmol) in 9.1 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was

allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 30 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by recrystallization from hot toluene to afford L-phenylalaninol[27] as a white solid.

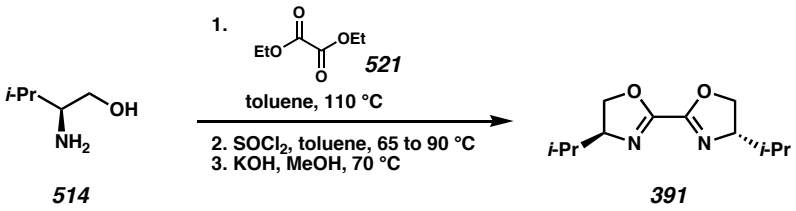
L-*tert*-Leucinol. To a suspension of $NaBH_4$ (692 mg, 18.3 mmol) in 18.3 mL THF at 23 °C was added L-*tert*-leucine (1.00 g, 7.62 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (1.93 g, 7.62 mmol) in 4.6 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 15 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude L-*tert*-leucinol[28] was carried on without further purification.



519 ***520***

(*R*)-Phenylglycinol. To a suspension of $NaBH_4$ (1.50 g, 39.6 mmol) in 40 mL THF at 23 °C was added (*R*)-(–)-phenylglycine (2.50 g, 16.5 mmol) in one portion. The resulting

suspension was cooled to 0 °C, and a solution of I_2 (4.19 g, 16.5 mmol) in 10 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 30 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by recrystallization from toluene to afford (*R*)-phenylglycinol[29] as a white solid.



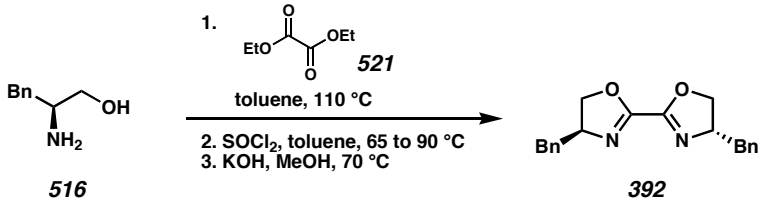
514 391

Bisoxazoline 391. Bisoxazoline **391** was synthesized according to a modified procedure of Denmark et al.[30] To a solution of L-valinol (500 μl, 4.49 mmol) in 32.9 mL toluene at 23 °C was added diethyl oxalate (291 μl, 2.14 mmol). The mixture was heated to 110 °C and stirred 6 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred overnight (8 h). The white diamide that precipitated (472 mg, 85% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (100 mg, 0.384 mmol) in 2.56 mL toluene at 65 °C was added $SOCl_2$ (61.6 μl, 0.845 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction

mixture was then cooled to room temperature and partitioned between EtOAc (50 mL) and brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

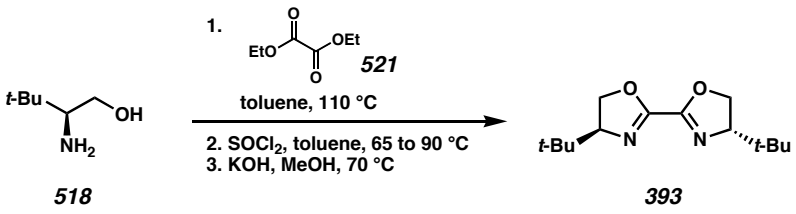
A suspension of the bis alkyl chloride (assume 0.384 mmol) and KOH (53.9 mg, 0.960 mmol) in 4.80 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 1 h, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (1:1 → 3:2 EtOAc/hexanes eluent) to provide the bisoxazoline[30] (74.1 mg, 86% over 2 steps, R_F = 0.42 in 2:1 hexanes/acetone) as a white solid.



Bisoxazoline 392. Bisoxazoline **392** was synthesized according to a modified procedure of Denmark et al.[30] To a solution of L-phenylalaninol (600 mg, 3.97 mmol) in 31.1 mL toluene at 23 °C was added diethyl oxalate (270 μl, 1.99 mmol). The mixture was heated to 110 °C and stirred 12 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred for 1 h. The white diamide that precipitated (548 mg, 77% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (548 mg, 1.54 mmol) in 11.0 mL toluene at 65 °C was added $SOCl_2$ (325 μl, 4.46 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and partitioned between EtOAc (150 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

A suspension of the bis alkyl chloride (assume 1.54 mmol) and KOH (216 mg, 3.85 mmol) in 19.3 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 1 h, and then it was cooled to room temperature and filtered through a plug of celite (1.5 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 50 mL CH_2Cl_2 and filtered through a plug of celite (1.5 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide the bisoxazoline[30] (300 mg, 61% over 2 steps, R_F = 0.14 in 1:1 hexanes/EtOAc) as a white solid.

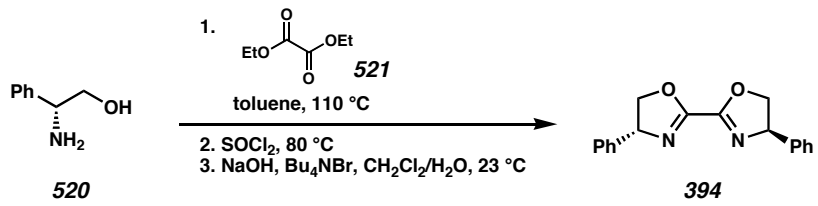


Bisoxazoline 393. Bisoxazoline **393** was synthesized according to a procedure analogous to that of Denmark et al.[30] To a solution of L-*tert*-leucinol (183 mg, 1.70 mmol) in 13.1 mL toluene at 23 °C was added diethyl oxalate (116 μl, 0.851 mmol). The mixture was

heated to 110 °C and stirred 10 h. After cooling to room temperature, 40 mL hexanes was added, and the mixture was stirred overnight (8 h). The white diamide that precipitated (147 mg, 60% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (88.5 mg, 0.307 mmol) in 2.05 mL toluene at 65 °C was added $SOCl_2$ (49.2 μl, 0.675 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was concentrated from PhH (3 x 15 mL) and carried directly to the next reaction.

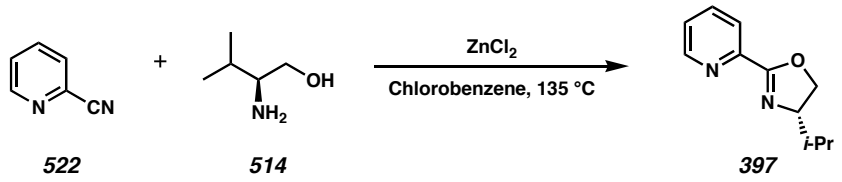
A suspension of the bis alkyl chloride (assume 0.307 mmol) and KOH (43.1 mg, 0.768 mmol) in 3.84 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 3 h, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide the bisoxazoline[31] (43.2 mg, 56% over 2 steps, R_F = 0.17 in 2:1 hexanes/EtOAc) as a white solid.



Bisoxazoline 394. To a solution of (*R*)-phenylglycinol (500 mg, 3.64 mmol) in 26.6 mL toluene at 23 °C was added diethyl oxalate (235 μl, 1.73 mmol). The mixture was heated to 110 °C and stirred 9 h. After cooling to room temperature, 100 mL hexanes was added, and the mixture was stirred 1 h. The white diamide that precipitated (447 mg, 79% yield) was collected by suction filtration and carried on to the subsequent reaction.

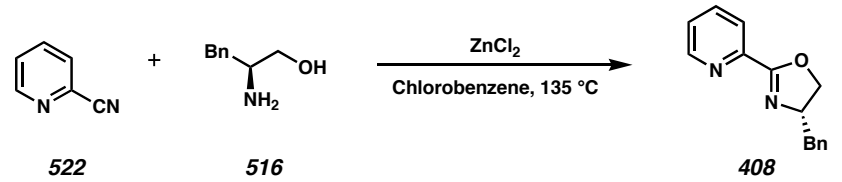
A solution of the diamide (431 mg, 1.31 mmol) in 6.0 mL $SOCl_2$ was stirred at 80 °C for 2 h. The bright yellow mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was concentrated from PhH (3 x 20 mL), and the crude material was taken directly to the next reaction.

Bisoxazoline formation was performed according to the procedure of Patra et al.[32] To a solution of NaOH (1.31 g, 32.8 mmol) in 4.0 mL H_2O and 26.2 mL CH_2Cl_2 at 23 °C was added Bu_4NBr (422 mg, 1.31 mmol). The mixture was stirred for 30 min, at which point the bis alkyl chloride (assume 1.31 mmol) was added portionwise over 5 min. The resulting mixture was stirred at 23 °C for 4 h. It was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/EtOAc eluent) to afford the bisoxazoline[32] (276 mg, 72% yield over 2 steps, R_F = 0.12 in 2:1 hexanes/EtOAc) as a white semisolid.



522 *514* *397*

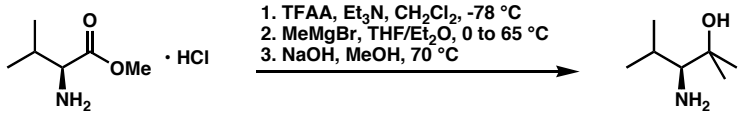
Oxazoline 397. Oxazoline **397** was synthesized according to the procedure of Bolm et al.[33] $ZnCl_2$ (8.2 mg, 0.0605 mmol) was flamed in a 50 mL round-bottom flask under vacuum. The flask was cooled to room temperature under nitrogen. It was then charged with L-valinol (200 μl, 1.81 mmol), chlorobenzene (3.63 mL), and 2-cyanopyridine (117 μl, 1.21 mmol), sequentially. The mixture was heated to 135 °C and stirred. After 6 h, the reaction was cooled to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between 125 mL CH_2Cl_2 and 75 mL H_2O. The organic phase was washed with H_2O (50 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (29:1 CH_2Cl_2/MeOH eluent) to provide the oxazoline[33] (207 mg, 90% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.



522 *516* *408*

Oxazoline 408. Oxazoline **408** was synthesized according to a procedure analogous to that of Bolm et al.[33] $ZnCl_2$ (14.2 mg, 0.104 mmol) was flamed in a 50 mL round-bottom flask under vacuum. The flask was cooled to room temperature under nitrogen. It was then charged with L-phenylalaninol (472 mg, 3.12 mmol), chlorobenzene (6.30 mL), and

2-cyanopyridine (200 μl, 2.08 mmol), sequentially. The mixture was heated to 135 °C and stirred. After 6 h, the reaction was cooled to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between 125 mL CH_2Cl_2 and 75 mL H_2O. The organic phase was washed with H_2O (50 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 EtOAc/hexanes w/ 1% Et_3N eluent) to provide the oxazoline[34] (437 mg, 88% yield, R_F = 0.03 in 1:1 hexanes/EtOAc) as an orange oil.

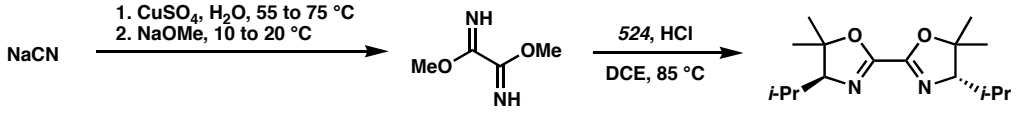


523 ***524***

Amino alcohol 524. Amino alcohol **524** was synthesized according to the procedure of Denmark et al.[30] To a suspension of L-valine methyl ester hydrochloride (1.00 g, 5.97 mmol) in 11.9 mL CH_2Cl_2 at 0 °C was added Et_3N (1.74 mL, 12.5 mmol) dropwise over 3 min. The mixture was maintained at 0 °C for 5 min, then cooled to –78 °C. Trifluoroacetic anhydride (860 μl, 6.09 mmol) was added over 1 min, and the resulting mixture was stirred at –78 °C. After 1 h, the reaction was quenched with saturated NH_4Cl (15 mL) and warmed to room temperature. Saturated $NaHCO_3$ (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the trifluoroacetamide (1.26 g, 93% yield, R_F = 0.75 in 1:1 hexanes/EtOAc), which was carried on to the next reaction.

To a solution of MeMgBr (9.43 mL, 3.0 M in Et_2O, 28.3 mmol) 9.43 mL in THF at 0 °C was added a solution of the trifluoroacetamide (1.26 g, 5.55 mmol) in 6.24 mL THF dropwise. The resulting mixture was heated to 65 °C and stirred 6 h. The reaction was then cooled to 0 °C, quenched with saturated NH_4Cl (75 mL), and extracted with EtOAc (4 x 75 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the tertiary alcohol (1.26 g, 100% yield, R_F = 0.50 in 2:1 hexanes/EtOAc), which was taken on to the subsequent reaction.

A solution of the tertiary alcohol (215 mg, 0.946 mmol) in 5% NaOH (w/v) in MeOH (1.89 mL) was heated to 70 °C. After 4 h, the mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (50 mL) and 1 M NaOH (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The amino alcohol[30] (**524**, R_F = 0.00 in 2:1 hexanes/EtOAc) was taken on to the next reaction without purification.



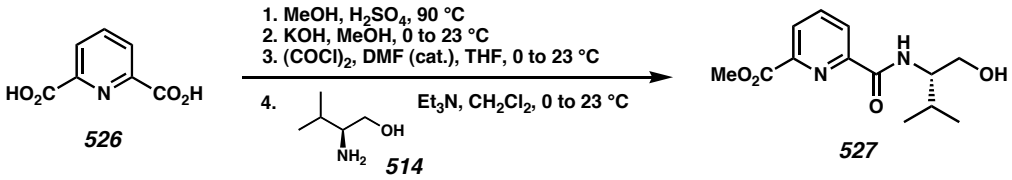
525 *413*

Bisoxazoline 413. Cyanogen was generated according to the procedure of Janz,[35] and the gas was trapped by methoxide according to the reported procedures.[36] To a solution of $CuSO_4$•$5H_2O$ (6.24 g, 25.0 mmol) in 25 mL H_2O at 55 °C was added a solution of NaCN (2.45 g, 50.0 mmol) in 50 mL H_2O dropwise via addition funnel over 40 min. The mixture was then heated to 75 °C and stirred an additional 30 min. The gas evolved over

the course of the reaction (cyanogen) was passed through a drying tube ($CaCl_2$) and bubbled directly into a solution of NaOMe in MeOH (50 mL, 0.5 M, 25.0 mmol, generated from Na metal in MeOH) at 10 °C. Once cyanogen evolution was complete, the methanol solution was concentrated to an oil, which was partitioned between brine (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. Bisimidate **525**[37] (435 mg, 24% yield, R_F = 0.32 in 2:1 hexanes/acetone) was carried directly to the next reaction without purification.

Bisoxazoline **413** was synthesized according to a procedure analogous to that of Ukaji et al.[38] To a solution of amino alcohol **524** (100 mg, 0.762 mmol) in 3.0 mL Et_2O at 0 °C was added HCl (400 μl, 0.800 mmol). The solvent was removed by rotary evaporation, and the white solid was dissolved in 1.50 mL dichloroethane. To this solution at 23 °C was added bisimidate **525** (43.4 mg, 0.374 mmol), and the resulting mixture was heated to 85 °C. After stirring for 24 h, the brown solution was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with H_2O (30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford the bisoxazoline (13.9 mg, 13% yield, R_F = 0.51 in 2:1 hexanes/acetone) as a white solid. **Bisoxazoline 413**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (d, *J* = 8.7 Hz, 2H), 1.95-1.79 (d of septets, *J* = 6.6, 8.7 Hz, 2H), 1.52 (s, 6H), 1.38 (s, 6H), 1.12 (d, *J* = 6.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 88.6, 81.0, 29.3, 29.0, 21.4, 21.2, 21.0; IR (film) 1615,

1089 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{28}O_2N_2]^+$: 280.2151, found 280.2154; $[\alpha]^{23}_D$ –55.60° (*c* 0.50, $CHCl_3$).



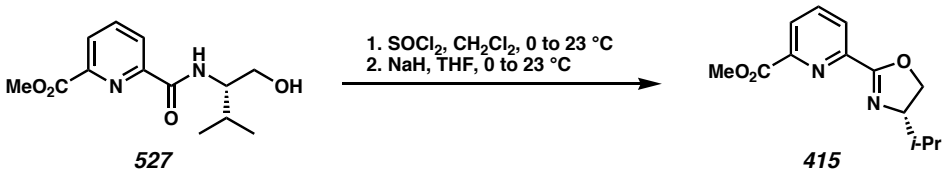
Amide 527. Esterification was performed according to the procedure of Chrystal et al.[39] To a suspension of 2,6-pyridinedicarboxylic acid (1.00 g, 5.98 mmol) in 12.5 mL MeOH at 23 °C was added 2.49 mL conc. H_2SO_4 dropwise. The reaction was heated to 90 °C and stirred for 40 h. The mixture was cooled to 0 °C, diluted with 10 mL H_2O, and quenched by adding Na_2CO_3 portionwise until bubbling ceased. The mixture was then reacidified with conc. HCl and extracted with $CHCl_3$ (4 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The bis methyl ester[39] (781 mg, 69% yield, R_F = 0.16 in 2:1 hexanes/EtOAc) was carried to the next reaction without further purification.

Monosaponification was performed according to a modified procedure of Hull et al.[40] To a suspension of the bis methyl ester (1.00 g, 5.12 mmol) in 34.1 mL MeOH at 0 °C was added KOH (287 mg, 5.12 mmol). The reaction was stirred at 0 °C for 3 h, then allowed to warm to 23 °C and stirred an additional 3 h. The solvent was then removed by rotary evaporation, and the residue was dissolved in H_2O (30 mL). Conc. HCl was added to acidify the mixture, and it was then extracted with $CHCl_3$ (4 x 50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was then dissolved in EtOAc (100 mL) and extracted with saturated $NaHCO_3$ (3 x 50 mL). The combined aqueous layers were acidified at 0 °C with conc. HCl and extracted with

$CHCl_3$ (4 x 75 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The mono methyl ester[40] (573 mg, 62% yield, R_F = 0.00 in 2:1 hexanes/EtOAc) was isolated as a white solid.

To a solution of the mono methyl ester (294 mg, 1.62 mmol) in 8.10 mL THF at 0 °C was added oxalyl chloride (707 μl, 8.10 mmol), then DMF (~20 μl). The mixture was stirred at 0 °C for 5 min, then allowed to warm to 23 °C. After 1 h, the mixture was concentrated in vacuo. The residue was concentrated from PhH (3 x 15 mL) and carried to the subsequent reaction.

To a solution of L-valinol (216 μl, 1.94 mmol) and Et_3N (677 μl, 4.86 mmol) in 8.20 mmol CH_2Cl_2 at 0 °C was added a solution of the crude acid chloride (assume 1.62 mmol) in 8.00 mL CH_2Cl_2 dropwise over 5 min. The mixture was maintained at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with 0.5 N HCl (30 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 EtOAc/hexanes → 9:1 EtOAc/MeOH eluent) to afford the amide (406 mg, 94% yield over 2 steps, R_F = 0.49 in 9:1 CH_2Cl_2/MeOH), which was carried on to the next reaction.

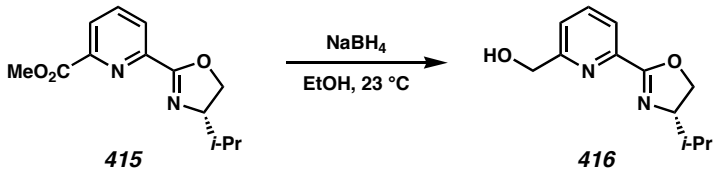


527 *415*

Oxazoline 415. To a solution of amide **527** (278 mg, 1.04 mmol) in 6.93 mL CH_2Cl_2 at 0 °C was added $SOCl_2$ (945 μl) dropwise. The reaction was allowed to warm to 23 °C and stirred. After 2 h, the mixture was quenched at 0 °C with H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 60 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc eluent) provided the alkyl chloride (258 mg, 87% yield, R_F = 0.70 in 3:1 EtOAc/hexanes) as a colorless oil.

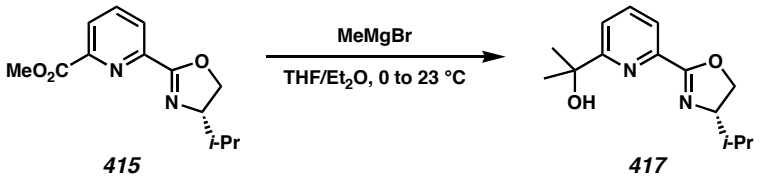
To a solution of the alkyl chloride (258 mg, 0.906 mmol) in 7.25 mL THF at 0 °C was added NaH (72.4 mg, 60% dispersion in mineral oil, 1.81 mmol). The mixture was stirred for 5 min at 0 °C, then allowed to warm to 23 °C. After 9 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl (30 mL), and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (3:1 EtOAc/hexanes eluent) to afford the oxazoline (144 mg, 64% yield, R_F = 0.26 in 3:1 EtOAc/hexanes) as a white solid. **Oxazoline 415**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.93 (app.t, *J* = 7.8 Hz, 1H), 4.55 (dd, *J* = 8.1, 9.6 Hz, 1H), 4.25 (app.t, *J* = 8.1 Hz, 1H), 4.20-4.11 (m, 1H), 4.00 (s, 3H), 1.88 (app.octet, *J* = 6.6 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 162.1, 148.2, 147.4, 137.9, 127.4, 126.9, 73.2, 71.3,

53.3, 33.1, 19.3, 18.5; IR (film) 1737, 1248 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{16}O_3N_2]^+$: 248.1161, found 248.1156; $[\alpha]^{23}_D$ –88.00° (*c* 1.0, $CHCl_3$).

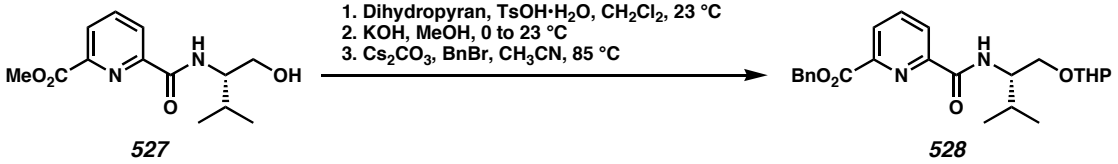


415 *416*

Oxazoline 416. To a solution of oxazoline **415** (45.3 mg, 0.182 mmol) in 1.82 mL EtOH at 23 °C was added $NaBH_4$ (31.1 mg, 0.822 mmol) portionwise over 3 min. The reaction was stirred at 23 °C for 2 h, and then it was quenched with 10 mL H_2O. The mixture was then partitioned between $CHCl_3$ (50 mL) and H_2O/brine (30 mL, 1:1), and the aqueous phase was extracted with $CHCl_3$ (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) afforded the alcohol (40.1 mg, 99% yield, R_F = 0.34 in 9:1 CH_2Cl_2/MeOH) as a colorless oil. **Oxazoline 416**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.77 (app.t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 4.85 (s, 2H), 4.49 (dd, *J* = 7.8, 9.0 Hz, 1H), 4.22 (app.t, *J* = 8.1 Hz, 1H), 4.19-4.11 (m, 1H), 1.90 (app.octet, *J* = 6.6 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 1H), 0.93 (6.9, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 160.4, 146.1, 137.5, 122.8, 122.7, 73.0, 70.9, 65.0, 32.9, 19.3, 18.3; IR (film) 3306, 2960, 1643, 1587, 1365 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{16}O_2N_2]^+$: 220.1212, found 220.1203; $[\alpha]^{23}_D$ –71.64° (*c* 0.50, $CHCl_3$).



Oxazoline 417. To a solution of MeMgBr (305 μl, 3.0 M in Et_2O, 0.915 mmol) in 1.03 mL THF at 0 °C was added a solution of oxazoline **415** (45.5 mg, 0.183 mmol) in 1.00 mL THF dropwise over 1 min. The reaction was maintained at 0 °C for 10 min, then allowed to warm to 23 °C. After 30 min, the mixture was quenched at 0 °C with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (29:1 CH_2Cl_2/MeOH eluent) to afford the tertiary alcohol (38.7 mg, 85% yield, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a colorless oil. **Oxazoline 417**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.78 (app.t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 4.51 (dd, *J* = 7.8, 9.3 Hz, 1H), 4.23 (app.t, *J* = 8.1 Hz, 1H), 4.20-4.13 (m, 1H), 1.91 (app.octet, *J* = 6.6 Hz, 1H), 1.57 (s, 3H), 1.56 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 162.8, 145.2, 137.7, 122.5, 121.0, 73.0, 72.1, 70.9, 33.0, 30.9, 30.8, 19.2, 18.4; IR (film) 2967, 1365, 965 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_2N_2]^+$: 248.1525, found 248.1533; $[\alpha]^{23}_D$ –82.40° (*c* 0.25, $CHCl_3$).

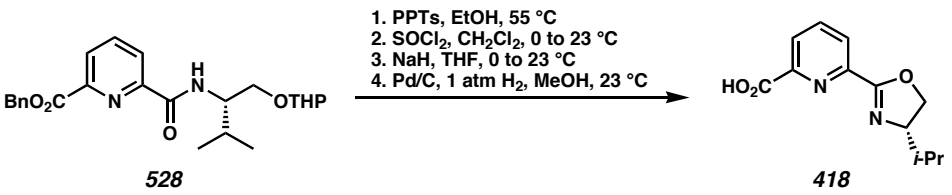


Ester 528. To a solution of amide **527** (80.3 mg, 0.302 mmol) and dihydropyran (30.3 μl, 0.332 mmol) in 1.51 mL CH_2Cl_2 at 23 °C was added TsOH•H_2O (0.6 mg, 0.00302

mmol). The solution was maintained at 23 °C for 11 h. The mixture was then diluted with 50 mL EtOAc and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) provided the THP ether (87.1 mg, 82% yield, R_F = 0.56 in 3:1 EtOAc/hexanes) as a colorless oil.

To a solution of the THP ether (87.1 mg, 0.249 mmol) in 860 μl MeOH at 0 °C was added a solution of KOH (27.9 mg, 0.498 mmol) in 800 μl MeOH. The resulting mixture was stirred at 0 °C for 30 min, then was allowed to warm to 23 °C. After 5 h, the MeOH was removed by rotary evaporation, and the residue was partitioned between $CHCl_3$ (50 mL) and H_2O/brine (30 mL, 1:1). The aqueous phase was extracted with $CHCl_3$ (4 x 25 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The carboxylic acid (R_F = 0.00 in 1:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

The benzyl ester was synthesized according to the procedure of Lee et al.[41] A suspension of the carboxylic acid (assume 0.249 mmol), Cs_2CO_3 (148 mg, 0.453 mmol), and BnBr (39.5 ml, 0.332 mmol) in 3.02 mL CH_3CN was heated to 85 °C. After 30 min, the reaction mixture was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_3CN eluent). The solvent was removed by rotary evaporation, and the residue was dissolved in 50 mL EtOAc and washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/EtOAc eluent) to afford the benzyl ester (74.3 mg, 70% yield over 2 steps, R_F = 0.47 in 1:1 hexanes/EtOAc), which was taken on to the subsequent reaction.



528 *418*

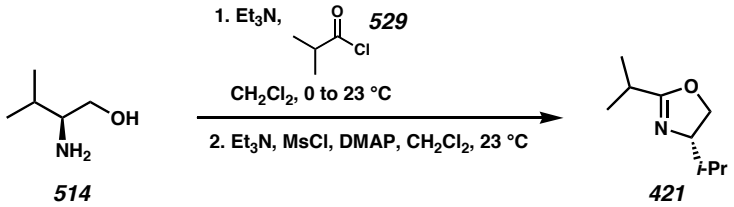
Oxazoline 418. To a solution of ester **528** (76.5 mg, 0.179 mmol) in 1.99 mL EtOH at 23 °C was added PPTs (4.5 mg, 0.0179 mmol). The reaction mixture was heated to 55 °C and stirred. After 2 h, the mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 EtOAc/hexanes eluent) afforded the alcohol (R_F = 0.13 in 1:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the alcohol (assume 0.179 mmol) in 1.31 mL CH_2Cl_2 at 0 °C was added $SOCl_2$ (179 μl) dropwise over 1 min. The reaction was maintained at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 2 h. The mixture was then quenched with 15 mL H_2O at 0 °C and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the alkyl chloride (54.5 mg, 84% yield over 2 steps, R_F = 0.58 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkyl chloride (207 mg, 0.574 mmol) in 4.59 mL THF at 0 °C was added NaH (45.9 mg, 60% dispersion in mineral oil, 1.15 mmol). The reaction was stirred at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 20 h. The mixture was then quenched at 0 °C with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL),

dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) afforded the oxazoline (88.1 mg, 47% yield, R_F = 0.25 in 1:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

A solution of the oxazoline (23.6 mg, 0.0728 mmol) and Pd/C (2.4 mg, 10%) in 2.91 mL MeOH at 23 °C was stirred under 1 atm H_2. After 15 min, the mixture was filtered through a plug of celite (pipet, MeOH eluent), and the filtrate was concentrated in vacuo. The crude material (R_F = 0.00 in 1:1 hexanes/EtOAc) was used immediately in the subsequent palladium reaction to avoid forming insoluble materials.

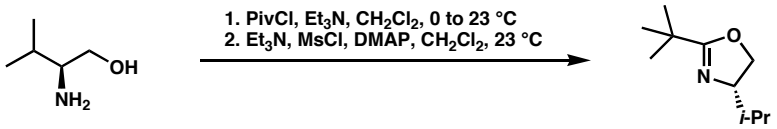


514 421

Oxazoline 421. To a solution of L-valinol (100 µl, 0.898 mmol) and *i*-Pr_2NEt (427 µl, 2.45 mmol) in 8.16 mL CH_2Cl_2 at 0 °C was added isobutyryl chloride (85.5 µl, 0.816 mmol). The reaction mixture was stirred for 5 min, then allowed to warm to 23 °C and stirred for 75 min. The reaction was then cooled to 0 °C, quenched with 0.5 N HCl (25 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude amide (63.2 mg, 45% yield, R_F = 0.13 in 1:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a solution of the amide (63.2 mg, 0.365 mmol) in 1.83 mL CH_2Cl_2 at 23 °C was added DMAP (4.5 mg, 0.0365 mmol), Et_3N (224 µl, 1.61 mmol), and MsCl (31.1 µl, 0.402 mmol), sequentially. The resulting mixture was stirred at 23 °C for 24 h. The

reaction was then partitioned between 50 mL CH_2Cl_2 and 30 mL saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with saturated $NaHCO_3$ (30 mL). The basic aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford the oxazoline[42] (7.0 mg, 12% yield, R_F = 0.64 in 2:1 hexanes/EtOAc) as a colorless oil.

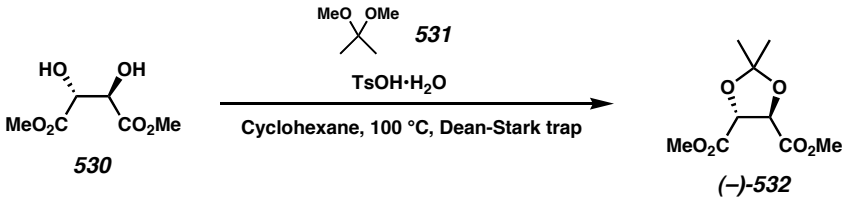


514 ***422***

Oxazoline 422. To a solution of L-valinol (100 μl, 0.898 mmol) and Et_3N (341 μl, 2.45 mmol) in 8.16 mL CH_2Cl_2 at 0 °C was added trimethylacetyl chloride (101 μl, 0.816 mmol). The reaction mixture was stirred for 5 min, then allowed to warm to 23 °C and stirred for 75 min. The reaction was then cooled to 0 °C, quenched with 0.5 N HCl (25 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude amide[43] (135 mg, 88% yield, R_F = 0.07 in 2:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

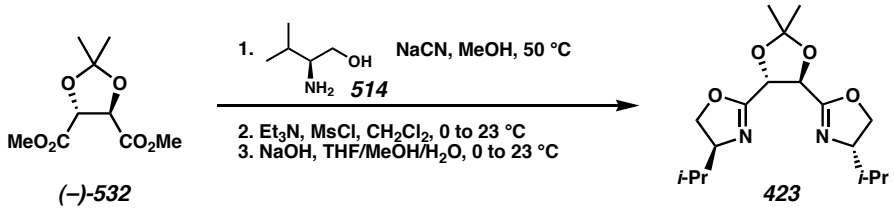
To a solution of the amide (135 mg, 0.721 mmol) in 3.61 mL CH_2Cl_2 at 23 °C was added DMAP (8.8 mg, 0.0721 mmol), Et_3N (442 μl, 3.17 mmol), and MsCl (61.4 μl, 0.793 mmol), sequentially. The resulting mixture was stirred at 23 °C for 24 h. The reaction was then partitioned between 50 mL CH_2Cl_2 and 30 mL saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases

were washed with saturated $NaHCO_3$ (30 mL). The basic aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford the oxazoline (61.0 mg, 50% yield, R_F = 0.64 in 2:1 hexanes/EtOAc) as a colorless oil. **Oxazoline 422**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 7.8, 9.3 Hz, 1H), 4.01 (app.t, *J* = 7.2 Hz, 1H), 3.99-3.92 (m, 1H), 1.89-1.78 (m, 1H), 1.23 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.1, 69.9, 33.5, 32.3, 28.1, 18.7, 17.4; IR (film) 2965, 1731, 1151 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{10}H_{19}NO]^+$: 169.1467, found 169.1479; $[\alpha]^{23}_D$ –18.64° (*c* 0.50, $CHCl_3$).



Acetonide (–)-532. Acetonide **(–)-532** was synthesized according to a modified procedure of Mash et al.[44] To a solution of dimethyl L-tartrate (500 mg, 2.81 mmol) and 2,2-dimethoxypropane (1.04 mL, 8.43 mmol) in 14 mL cyclohexane was added TsOH•H_2O (53.5 mg, 0.281 mmol). The reaction was heated to 100 °C with azeotropic removal of MeOH via a Dean-Stark trap. The mixture turned dark red over the course of the reaction (16 h). The mixture was then cooled to room temperature, and 100 mg K_2CO_3 was added. The solution was stirred for 1.5 h (red color dissipated to pale yellow), and then it was partitioned between EtOAc (100 mL) and saturated $NaHCO_3/H_2O$ (60 ml, 1:2). The aqueous phase was extracted with EtOAc (50 mL), and

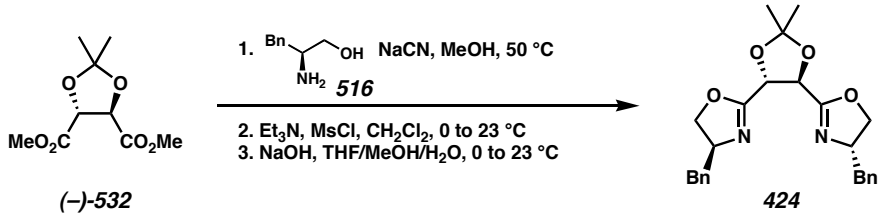
the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) provided the acetonide[44] (602 mg, 98% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a yellow oil.



Bisoxazoline 423. The synthesis of bisoxazoline **423** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (103 mg, 0.472 mmol) and L-valinol (116 μl, 1.04 mmol) in 1.57 mL MeOH at 50 °C was added NaCN (2.3 mg, 0.0472 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.02 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.472 mmol) and Et_3N (295 μl, 2.12 mmol) in 2.15 mL CH_2Cl_2 at 0 °C was added MsCl (91.3 μl, 1.18 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.21 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.472 mmol) in THF (2.43 mL), MeOH (2.78 mL), and H_2O (2.78 mL) at 0 °C was added NaOH (56.8 mg, 1.42 mmol). The mixture was stirred at 0 °C for 2 h, then allowed to warm to 23 °C and stirred for an additional 4 h. The reaction was then cooled to 0 °C, quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (3:2 hexanes/EtOAc w/ 1% Et_3N eluent) to afford the bisoxazoline[45] (49.7 mg, 32% yield over 3 steps, R_F = 0.37 in 1:1 hexanes/EtOAc) as a colorless oil.

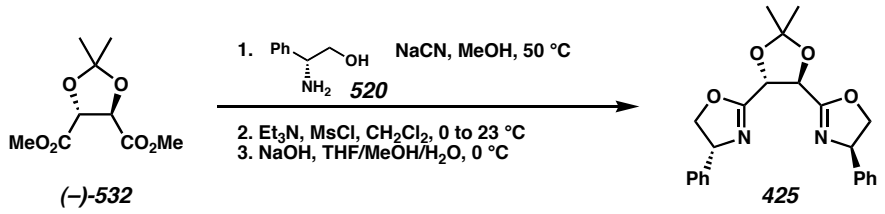


Bisoxazoline 424. Bisoxazoline **424** was synthesized according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (85.2 mg, 0..390 mmol) and L-phenylalaninol (130 mg, 0.858 mmol) in 1.30 mL MeOH at 50 °C was added NaCN (1.9 mg, 0.0390 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.390 mmol) and Et_3N (245 μl, 1.76 mmol) in 1.77 mL CH_2Cl_2 at 0 °C was added MsCl (75.5 μl, 0.975 mmol) dropwise over 1 min.

The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.25 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.390 mmol) in THF (2.01 mL), MeOH (2.29 mL), and H_2O (2.29 mL) at 0 °C was added NaOH (46.8 mg, 1.17 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (3:2 hexanes/EtOAc w/ 1% Et_3N eluent) to afford the bisoxazoline[45] (87.9 mg, 54% yield over 3 steps, R_F = 0.51 in 3:1 EtOAc/hexanes) as a colorless oil.

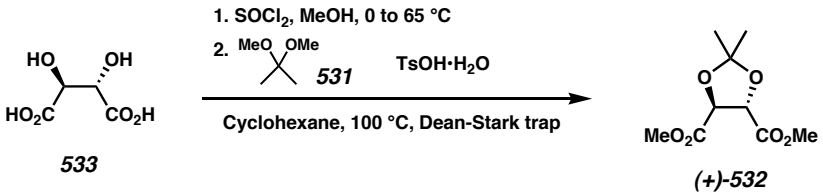


Bisoxazoline 425. The synthesis of bisoxazoline **425** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (103 mg, 0.472 mmol) and (*R*)-phenylglycinol (136 mg, 0.991 mmol) in 3.75 mL MeOH at 50 °C was added NaCN (4.3 mg, 0.0661 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and

30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.05 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.472 mmol) and Et_3N (296 μl, 2.12 mmol) in 2.15 mL CH_2Cl_2 at 0 °C was added MsCl (91.3 μl, 1.18 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.33 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

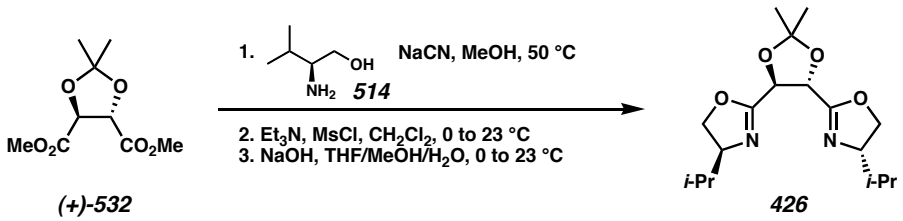
To a solution of the bis mesylate (assume 0.472 mmol) in THF (2.43 mL), MeOH (2.78 mL), and H_2O (2.78 mL) at 0 °C was added NaOH (56.8 mg, 1.42 mmol). The mixture was stirred at 0 °C for 2.5 h. The reaction was then quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **425** (88.0 mg, 47% yield over 3 steps, R_F = 0.79 in 3:1 EtOAc/hexanes) as a colorless oil. The spectroscopic data, with the exception of the sign of optical rotation, were identical to the reported information for the opposite enantiomer.[46]



Acetonide (+)-532. Dimethyl D-tartrate was synthesized according to the procedure of Kim et al.[47] To a solution of D-tartaric acid (500 mg, 3.33 mmol) in 1.67 mL MeOH at 0 °C was added $SOCl_2$ (1.26 mL, 17.3 mmol) dropwise over 2 min. The mixture was maintained at 0 °C for 1 h, then heated to 65 °C. After 3 h, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ (30 mL). The solvent was removed by rotary evaporation, and the aqueous residue was extracted with EtOAc (4 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Dimethyl D-tartrate (515 mg, 87% yield, R_F = 0.02 in 4:1 hexanes/EtOAc) was carried on to the subsequent reaction without further purification.

Acetonide **(+)-532** was synthesized according to a modified procedure of Mash et al.[44] To a solution of dimethyl D-tartrate (515 mg, 2.89 mmol) and 2,2-dimethoxypropane (1.07 mL, 8.67 mmol) in 14 mL cyclohexane was added TsOH•H_2O (55.0 mg, 0.289 mmol). The reaction was heated to 100 °C with azeotropic removal of MeOH via a Dean-Stark trap. The mixture turned dark red over the course of the reaction (16 h). The mixture was then cooled to room temperature, and 100 mg K_2CO_3 was added. The solution was stirred for 1.5 h (red color dissipated to pale yellow), and then it was partitioned between EtOAc (100 mL) and saturated $NaHCO_3/H_2O$ (60 ml, 1:2). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash

chromatography (4:1 hexanes/EtOAc eluent) provided the acetonide[44] (624 mg, 99% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a yellow oil.

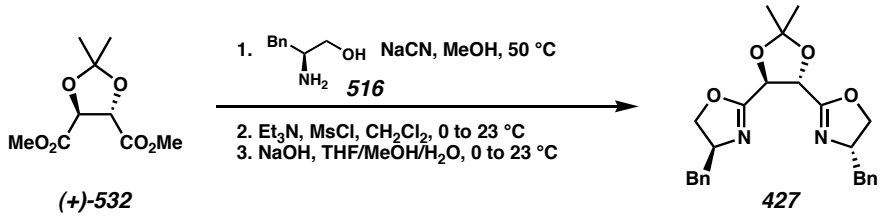


Bisoxazoline 426. The synthesis of bisoxazoline **426** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(+)-532** (112 mg, 0.513 mmol) and L-valinol (126 μl, 1.13 mmol) in 1.71 mL MeOH at 50 °C was added NaCN (2.5 mg, 0.0513 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.513 mmol) and Et_3N (322 μl, 2.31 mmol) in 2.33 mL CH_2Cl_2 at 0 °C was added MsCl (99.1 μl, 1.28 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.21 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.513 mmol) in THF (2.64 mL), MeOH (3.02 mL), and H_2O (3.02 mL) at 0 °C was added NaOH (61.6 mg, 1.54 mmol). The

mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **426**[45] (96.8 mg, 58% yield over 3 steps, R_F = 0.57 in 3:1 EtOAc/hexanes) as a white solid.

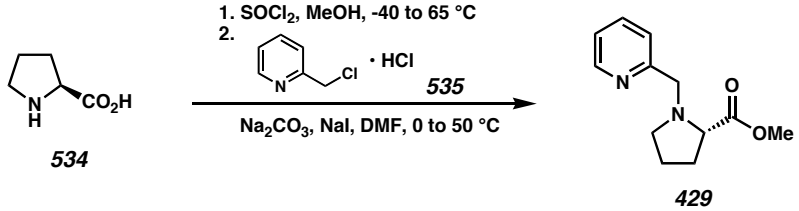


Bisoxazoline 427. Bisoxazoline **427** was synthesized according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(+)-532** (110 mg, 0.504 mmol) and L-phenylalaninol (168 mg, 1.11 mmol) in 1.68 mL MeOH at 50 °C was added NaCN (2.5 mg, 0.0504 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.504 mmol) and Et_3N (316 μl, 2.27 mmol) in 2.29 mL CH_2Cl_2 at 0 °C was added MsCl (97.5 μl, 1.26 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over

Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.26 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

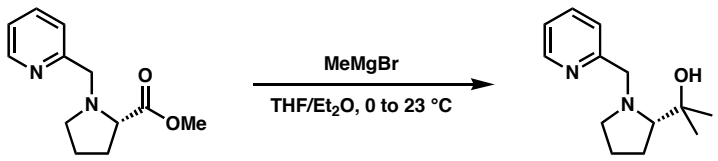
To a solution of the bis mesylate (assume 0.504 mmol) in THF (2.60 mL), MeOH (2.96 mL), and H_2O (2.96 mL) at 0 °C was added NaOH (60.4 mg, 1.51 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 → 1:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **427** (103 mg, 49% yield over 3 steps, R_F = 0.57 in 3:1 EtOAc/hexanes) as a colorless oil. **Bisoxazoline 427**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (comp m, 10H), 4.96 (s, 2H), 4.53-4.43 (m, 2H), 4.29 (app.t, *J* = 9.0 Hz, 2H), 4.09 (dd, *J* = 7.2, 8.4 Hz, 2H), 3.15 (dd, *J* = 5.1, 13.8 Hz, 2H), 2.67 (dd, *J* = 8.4, 13.8 Hz, 2H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 137.7, 129.5, 128.8, 126.8, 112.9, 74.1, 72.7, 67.6, 41.5, 26.4; IR (film) 1667, 976 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{25}H_{28}O_4N_2]^+$: 420.2049, found 420.2068; $[\alpha]^{23}_D$ +29.22° (*c* 1.0, $CHCl_3$).



Ester 429. L-Proline methyl ester hydrochloride was synthesized according to the procedure of Xin et al.[48] To a solution of L-proline (100 mg, 0.869 mmol) in 869 μl

MeOH at –40 °C was added $SOCl_2$ (87.5 μl, 1.20 mmol). The reaction mixture was allowed to warm to 23 °C, then heated to 65 °C. After 1.5 h, the reaction was cooled to room temperature, and the solvent was removed by rotary evaporation. The crude residue was concentrated from MeOH (2 x 10 mL) and the ester hydrochloride salt (R_F = 0.10 in 9:1 CH_2Cl_2/MeOH) was carried on to the subsequent reaction without further purification.

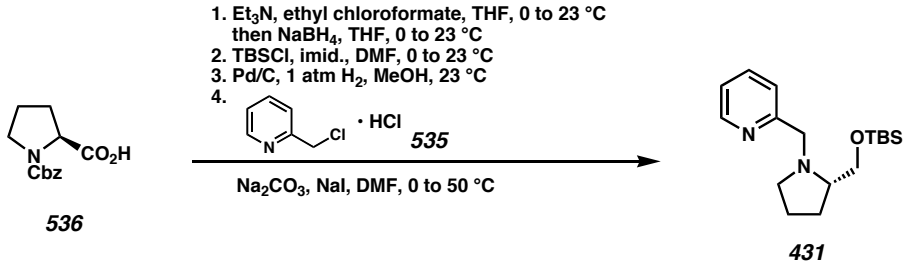
Ester **429** was synthesized according to the procedure of Chelucci et al.[49] To a solution of L-proline methyl ester hydrochloride (assume 0.869 mmol), 2-picolyl chloride hydrochloride (95.0 mg, 0.579 mmol), and NaI (4.3 mg, 0.0290 mmol) in 1.35 mL DMF at 0 °C was added Na_2CO_3 (220 mg, 2.08 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (3:1 EtOAc/hexanes w/ 1% Et_3N eluent) afforded alkylated proline methyl ester **429**[49] (120 mg, 94% yield, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil.



429 *430*

Alcohol 430. The synthesis of tertiary alcohol **430** was performed according to the procedure of Chelucci et al.[49] To a solution of MeMgBr (653 ml, 3.0 M in Et_2O, 1.96 mmol) in 327 μl THF at 0 °C was added a solution of methyl ester **429** (108 mg, 0.490

mmol) in 522 μl THF dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then quenched with 1 N HCl 10 mL and stirred an additional 1 h. Aqueous NaOH (10%, 30 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, filtered through a pad of celite (CH_2Cl_2 eluent), dried over K_2CO_3, and concentrated to an oil. The residue was purified by flash chromatography (9:1 CH_2Cl_2/MeOH eluent) to provide the tertiary alcohol[49] (94.4 mg, 87% yield, R_F = 0.22 in 9:1 CH_2Cl_2/MeOH) as a yellow oil.



Pyrrolidine 431. Carboxylic acid reduction was performed according to the procedure of Seijas et al.[50] To a solution of *N*-carbobenzyloxy-L-proline (800 mg, 3.21 mmol) in 8.23 mL THF at 0 °C was added Et_3N (581 μl, 4.17 mmol). After 35 min at 0 °C, ethyl chloroformate (368 μl, 3.85 mmol) was added. The mixture was allowed to warm to 23 °C and stirred 45 min. The mixture was then cooled back to 0 °C, and a solution of $NaBH_4$ (243 mg, 6.42 mmol) in 5.44 mL H_2O was added dropwise. The reaction was allowed to warm to 23 °C and stirred overnight (8 h). The reaction mixture was then quenched at 0 °C with saturated NH_4Cl (20 mL), and 1 N HCl was added until the solution was slightly acidic (pH = 5). The THF was removed by rotary evaporation, and the residue was partitioned between H_2O (30 mL) and EtOAc (150 mL). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic layers were washed

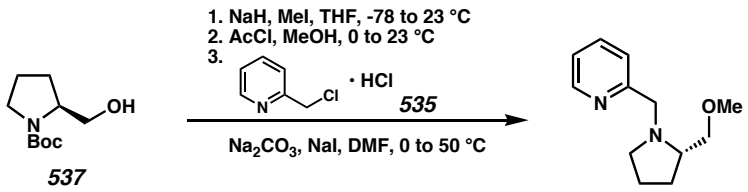
with 10% aq. NaOH (50 mL) and then brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide the alcohol[50] (653 mg, 86% yield, R_F = 0.10 in 2:1 hexanes/EtOAc), which was carried directly to the subsequent reaction.

Silylation and carbamate cleavage were performed according to the procedure of Vedejs and Lee.[51] To a solution of the alcohol (336 mg, 1.43 mmol) in 3.98 mL DMF at 23 °C was added imidazole (244 mg, 3.58 mmol). The mixture was then cooled to 0 °C, and TBSCl (259 mg, 1.72 mmol) was added. The reaction was allowed to warm to 23 °C and stirred. After 2 h, the mixture was diluted with 100 mL Et_2O and washed with 1 N HCl (2 x 30 mL), then brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford the silyl ether (450 mg, 90% yield, R_F = 0.76 in 2:1 hexanes/EtOAc), which was taken to the next reaction.

A mixture of the silyl ether (79.3 mg, 0.227 mmol) and Pd/C (2.3 mg, 10%) in 2.27 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 1 h, the suspension was filtered through a plug of celite (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The crude pyrrolidine[51] (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried to the subsequent reaction without purification.

Pyrrolidine alkylation was performed according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine (assume 0.227 mmol), 2-picolyl chloride hydrochloride (37.2 mg, 0.227 mmol), and NaI (1.7 mg, 0.0114 mmol) in 535 μl DMF at 0 °C was added Na_2CO_3 (50.6 mg, 0.477 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room

temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) afforded alkylated pyrrolidine **431** (51.2 mg, 74% yield over 2 steps, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil. **Pyrrolidine 431**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br d, *J* = 4.5 Hz, 1H), 7.64 (br t, *J* = 7.8 Hz, 1H), 7.50-7.43 (br m, 1H), 7.14 (br t, *J* = 6.0 Hz, 1H), 4.25 (br d, *J* = 13.5 Hz, 1H), 3.66 (br, 2H), 3.50 (br, 1H), 3.00 (br, 1H), 2.77 (br, 1H), 2.34 (br, 1H), 2.00-1.88 (br m, 1H), 1.72 (br, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 136.5, 123.2, 122.0, 67.2, 65.7, 62.0, 55.2, 28.5, 26.2, 23.3, 18.5, -5.1, -5.1; IR (film) 2954, 1088, 836 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{17}H_{31}ON_2Si]^+$: 307.2206, found 307.2202; $[\alpha]^{23}_D$ –65.12° (*c* 0.25, $CHCl_3$).

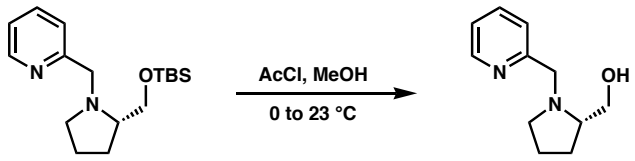


Pyrrolidine 432. Methylation of *N*-*t*-Boc-L-prolinol was performed according to the procedure of Kurokawa et al.[52] To a solution of *N*-*t*-Boc-L-prolinol (400 mg, 1.99 mmol) in 7.96 mL THF at –78 °C was added MeI (215 μl, 3.42 mmol), then NaH (134 mg, 60% dispersion in mineral oil, 3.34 mmol). The reaction was allowed to warm to 23 °C over 1 h. The mixture was then quenched at 0 °C with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (6:1

hexanes/EtOAc eluent) to provide the methyl ether[52] (401 mg, 93% yield, R_F = 0.60 in 2:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

Anhydrous HCl was generated by addition of 2.45 mL AcCl dropwise slowly to 7.91 mL MeOH at 0 °C. After 3 min, a solution of the methyl ether (120 mg, 0.557 mmol) in 1.00 mL MeOH was added. The resulting mixture was stirred for 5 min, then allowed to warm to 23 °C. After 90 min, the solution was concentrated in vacuo, and the crude hydrochloride salt (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

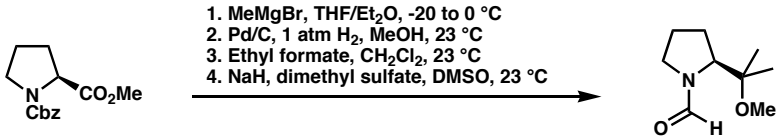
To a solution of the pyrrolidine hydrochloride salt (assume 0.557 mmol), 2-picolyl chloride hydrochloride (91.4 mg, 0.557 mmol), and NaI (4.0 mg, 0.0279 mmol) in 1.31 mL DMF at 0 °C was added Na_2CO_3 (183 mg, 1.73 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc w/ 1% Et_3N eluent) afforded alkylated pyrrolidine **432**[49] (95.2 mg, 83% yield over 2 steps, R_F = 0.19 in 9:1 CH_2Cl_2/MeOH) as an orange oil.



431 *433*

Alcohol 433. Anhydrous HCl was generated by addition of 3.15 mL AcCl dropwise slowly to 47.4 mL MeOH at 0 °C. After 3 min, a solution of pyrrolidine **431** (315 mg,

1.03 mmol) in 47.4 mL MeOH was added to the HCl solution. The mixture was allowed to warm to 23 °C and stirred. After 1 h, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ (50 mL). The MeOH was removed by rotary evaporation, and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, dried over K_2CO_3, and concentrated to an oil. The residue was purified by flash chromatography (19:1 → 3:1 CH_2Cl_2/MeOH eluent) to afford the primary alcohol[49] (138 mg, 70% yield, R_F = 0.11 in 9:1 CH_2Cl_2/MeOH) as an orange oil.



538 *539*

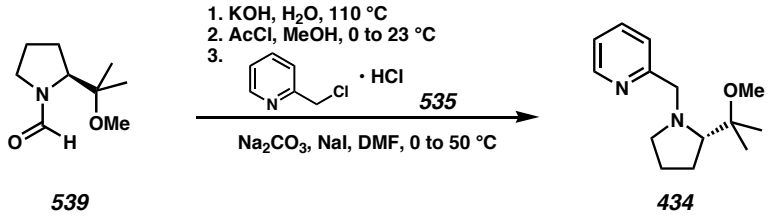
Pyrrolidine 539. *N*-formyl pyrrolidine **539** was synthesized according to the procedure of Nakayama and Thompson.[53] To a solution of *N*-carbobenzyloxy-L-proline methyl ester (500 μl, 2.23 mmol) in 3.34 mL THF at –20 °C was added MeMgBr (2.23 mL, 3.0 M in Et_2O, 6.69 mmol) dropwise over 5 min. The reaction was maintained at –20 °C for 30 min, then warmed to 0 °C and stirred for an additional 1 h. The mixture was then quenched with saturated NH_4Cl (30 mL) and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc eluent) afforded the tertiary alcohol (549 mg, 93% yield, R_F = 0.26 in 2:1 hexanes/EtOAc), which was taken on to the subsequent reaction.

A mixture of the tertiary alcohol (549 mg, 2.08 mmol) and Pd/C (20.8 mg, 10%) in 20.8 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 1 h, the suspension was filtered through a plug of celite (1.5 x 5 cm, Et_2O eluent), and the filtrate was

concentrated in vacuo. The crude pyrrolidine (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried to the subsequent reaction without purification.

To a solution of the crude pyrrolidine (assume 2.08 mmol) in 1.30 mL CH_2Cl_2 at 23 °C was added ethyl formate (1.03 mL, 12.7 mmol). The reaction was maintained at 23 °C for 45 h. The mixture was then concentrated to an oil, and the residue was dissolved in 30 mL EtOAc and passed through a plug of SiO_2 (1 x 5 cm, EtOAc eluent). The filtrate was concentrated in vacuo, and the product formamide (248 mg, 76% yield over 2 steps) was carried on to the next reaction without further purification.

Sodium dimsylate was generated by adding NaH (350 mg, 60% dispersion in mineral oil, 8.75 mmol) to 3.40 mL DMSO and heating the mixture at 70 °C for 1 h. To a solution of the formamide (248 mg, 1.58 mmol) and triphenylmethane (5 mg) in 1.58 mL DMSO at 23 °C was added the sodium dimsylate solution dropwise. Once the red color persisted, dimethyl sulfate (165 μl, 1.74 mmol) was added. The mixture was stirred at 23 °C for 90 min, and then it was quenched with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 EtOAc/hexanes → 100% EtOAc eluent) to afford the tertiary methyl ether[53] (225 mg, 99% yield, R_F = 0.35 in 100% EtOAc), which was taken to the next reaction.

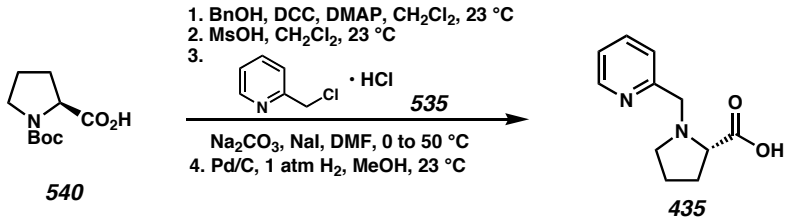


Pyrrolidine 434. Deformylation of **539** was performed according to the procedure of Nakayama and Thompson.[53] A solution of formamide **539** (75.4 mg, 0.440 mmol) in aqueous KOH (10%, 942 μl) was heated at 110 °C. After 1.5 h, the reaction was cooled to room temperature and extracted with CH_2Cl_2 (5 x 20 mL). The combined organic phases were dried over K_2CO_3 and concentrated to an oil. The pyrrolidine (R_F = 0.00 in 100% EtOAc) was carried to the subsequent reaction.

Anhydrous HCl was generated by addition of 156 μl AcCl (2.20 mmol) dropwise slowly to 2.20 mL MeOH at 0 °C. After 3 min, a solution of the pyrrolidine (assume 0.440 mmol) in 2.20 mL MeOH was added. The resulting mixture was stirred for 5 min, then allowed to warm to 23 °C. After 30 min, the solution was concentrated in vacuo, concentrated from PhH (3 x 15 mL), and the crude hydrochloride salt was carried directly to the subsequent reaction.

The pyrrolidine alkylation was performed according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine hydrochloride salt (assume 0.440 mmol), 2-picolyl chloride hydrochloride (72.2 mg, 0.440 mmol), and NaI (3.3 mg, 0.0220 mmol) in 1.04 mL DMF at 0 °C was added Na_2CO_3 (144 mg, 1.36 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc w/ 1% Et_3N

eluent) afforded alkylated pyrrolidine **434** (69.2 mg, 67% yield over 3 steps, R_F = 0.30 in 9:1 CH_2Cl_2/MeOH) as a yellow oil. **Pyrrolidine 434**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br d, *J* = 4.5 Hz, 1H), 7.65 (br t, *J* = 6.9 Hz, 1H), 7.55 (br d, *J* = 7.5 Hz, 1H), 7.12 (br t, *J* = 5.7 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.63 (br d, *J* = 14.7 Hz, 1H), 3.22 (s, 3H), 2.99-2.84 (br m, 2H), 2.38-2.28 (br m, 1H), 1.92-1.82 (br m, 3H), 1.22 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 136.5, 122.7, 121.7, 70.3, 63.9, 55.8, 49.3, 28.0, 24.4, 22.0, 21.4; IR (film) 2970, 1146 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{23}N_2O]^+$: 235.1810, found 235.1821; $[\alpha]^{23}_D$ –77.04° (*c* 0.25, $CHCl_3$).

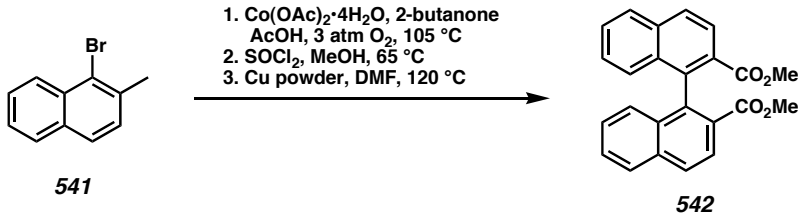


Carboxylic acid 435. Esterification was performed according to the procedure of Gardner and Gellman.[54] To a solution of *N*-*t*-Boc-L-proline (200 mg, 0.929 mmol) in 4.65 mL CH_2Cl_2 at 23 °C (maintained with an external water bath) was added DCC (229 mg, 1.11 mmol), DMAP (13.6 mg, 0.111 mmol), and BnOH (207 μl, 2.00 mmol), sequentially. The resulting heterogeneous mixture was stirred at 23 °C for 2 h. The mixture was suction-filtered through a pad of celite (5 x 5 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford the benzyl ester[54] (R_F = 0.48 in 2:1 hexanes/EtOAc) contaminated with benzyl alcohol. The mixture was carried on without further purification.

To a solution of the benzyl ester mixture (assume 0.929 mmol) in 2.32 mL CH_2Cl_2 at 23 °C was added methanesulfonic acid (229 μl, 3.53 mmol) dropwise over 1 min. The reaction mixture was maintained at 23 °C for 5 min, then cooled to 0 °C and quenched with saturated $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 40 mL), and the combined organic layers were dried over K_2CO_3 and concentrated to an oil. This residue was partitioned between 30 mL 0.5 N HCl and 30 mL Et_2O to separate the benzyl alcohol from the previous step. The organic phase was extracted with 0.5 N HCl (2 x 20 mL), and the combined aqueous phases were basified with solid Na_2CO_3. The mixture was then extracted with CH_2Cl_2 (3 x 40 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. The benzyl ester (121 mg, 63% yield over 2 steps, R_F = 0.00 in 2:1 hexanes/EtOAc) was sufficiently pure to be taken to the next reaction.

The pyrrolidine was alkylated according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine benzyl ester (78.2 mg, 0.381 mmol), 2-picolyl chloride hydrochloride (56.8 mg, 0.346 mmol), and NaI (2.6 mg, 0.0173 mmol) in 816 μl DMF at 0 °C was added Na_2CO_3 (80.7 mg, 0.761 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 4 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 → 3:1 EtOAc/hexanes eluent) afforded the alkylated pyrrolidine (97.0 mg, 95% yield, R_F = 0.44 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil.

A mixture of the benzyl ester (34.0 mg, 0.115 mmol) and Pd/C (3.4 mg, 10%) in 4.60 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 45 min, the suspension was filtered through a plug of celite (1.5 x 5 cm, MeOH eluent), and the filtrate was concentrated in vacuo. The crude carboxylic acid (23.7 mg, 100% yield, R_F = 0.00 in 9:1 CH_2Cl_2/MeOH) was sufficiently pure to be used in the next reaction. **Carboxylic acid 435**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.64 (d, *J* = 5.1 Hz, 1H), 7.87 (app.t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 5.1, 7.8 Hz, 1H), 4.61 (d, *J* = 14.1 Hz, 1H), 4.40 (d, *J* = 14.1 Hz, 1H), 4.07 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.72 (ddd, *J* = 4.5, 7.2, 11.4 Hz, 1H), 3.22 (ddd, *J* = 7.2, 8.7, 11.4 Hz, 1H), 2.52-2.40 (m, 1H), 2.25-1.94 (comp m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 154.4, 149.6, 137.5, 124.0, 123.6, 68.0, 59.4, 54.6, 29.8, 24.3; IR (film) 3400, 1631 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{15}N_2O_2]^+$: 207.1134, found 207.1142; $[\alpha]^{23}_D$ –46.22° (*c* 1.0, MeOH).



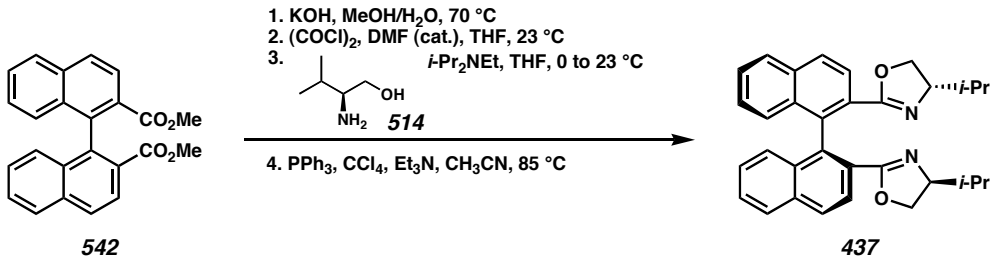
541 ***542***

Binaphthyl 542. Binaphthyl **542** was synthesized according to the procedure of Seki et al.[55] A solution of 1-bromo-2-methylnaphthalene (1.00 mL, 6.42 mmol), 2-butanone (173 μl, 1.93 mmol), and $Co(OAc)_2$•$4H_2O$ (319 mg, 1.28 mmol) in 5.35 mL AcOH under 3 atm O_2 was heated to 105 °C. The mixture was stirred overnight (10 h), then cooled to room temperature and partitioned between 100 mL EtOAc and 50 mL 1 N HCl. The aqueous phase was extracted with EtOAc (75 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash

chromatography (7:1 CH_2Cl_2/MeOH eluent) to afford the carboxylic acid[55] (1.48 g, 92% yield, R_F = 0.07 in 4:1 hexanes/EtOAc) as a brown solid.

To a solution of the carboxylic acid (206 mg, 0.820 mmol) in 683 μl MeOH at 23 °C was added $SOCl_2$ (71.8 μl, 0.984 mmol) dropwise over 1 min. The reaction was heated to 65 °C and stirred 3 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between 50 mL EtOAc and 30 mL H_2O, and the organic phase was washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude methyl ester[56] (R_F = 0.42 in 4:1 hexanes/EtOAc) was taken directly to the subsequent reaction without purification.

A solution of the methyl ester (assume 0.820 mmol) and Cu powder (88.3 mg, 1.39 mmol) in 293 μl DMF was heated to 120 °C for 2 h. The mixture was then cooled to room temperature, diluted with 30 mL CH_2Cl_2, and filtered through a pad of celite (2 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was partitioned between H_2O (30 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (30 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc) to provide **542**[56] (127 mg, 90% yield over 2 steps, R_F = 0.25 in 4:1 hexanes/EtOAc).



542 *437*

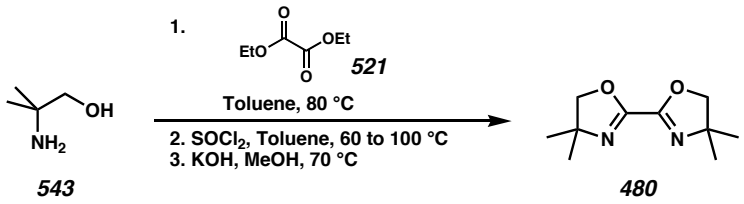
Bisoxazoline 437. The saponification of **542** was performed according to the procedure of Seki et al.[55] To a solution of the bis methyl ester (480 mg, 1.30 mmol) in 3.61 mL MeOH and 722 μl H_2O at 23 °C was added KOH (263 mg, 4.68 mmol). The reaction was heated to 70 °C and stirred for 2 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between H_2O (60 mL) and toluene (60 mL). The organic phase was extracted with 3 N NaOH (50 mL), and the combined aqueous phases were acidified with conc. HCl and extracted with EtOAc (3 x 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The bis carboxylic acid[55] (411 mg, 92% yield, R_F = 0.00 in 1:1 hexanes/EtOAc) was carried on directly to the next reaction without purification.

Bisoxazoline **437** was synthesized according to a modified procedure of Uozumi et al.[57] To a solution of the bis carboxylic acid (97.4 mg, 0.285 mmol) in 1.43 mL THF at 23 °C was added oxalyl chloride (125 μl, 1.43 mmol), then DMF (~10 μl). The reaction was stirred at 23 °C for 90 min. The mixture was then concentrated in vacuo, and the residue was concentrated from PhH (2 x 15 mL). The bis acid chloride was taken on to the next reaction.

To a solution of L-valinol (94.2 μl, 0.855 mmol) and Et_3N (119 μl, 0.855 mmol) in 1.00 mL THF at 0 °C was added a solution of the bis acid chloride (assume 0.285

mmol) in 600 μl THF dropwise over 1 min. The mixture was allowed to warm to 23 °C and stirred. After 1 h, the mixture was concentrated to an oil, which was dissolved in 50 mL EtOAc. The solution was washed sequentially with 0.5 N HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude diamide (R_F = 0.40 in 7:1 CH_2Cl_2/MeOH) as a mix of diastereomers was taken directly to the subsequent reaction.

To a solution of PPh_3 (194 mg, 0.741 mmol), CCl_4 (179 μl, 1.85 mmol), and Et_3N (139 μl, 0.998 mmol) in1.85 mL CH_3CN at 23 °C was added a solution of the diamide (assume 0.285 mmol) in 1.00 mL CH_3CN. The resulting mixture was heated to 85 °C and stirred for 3 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was dissolved in 50 mL EtOAc and washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (2 columns: 6:1 hexanes/EtOAc, then 9:1 → 3:1 CH_2Cl_2/EtOAc eluent) to provide the diastereomerically and enantiomerically pure (*S,S*)-bisoxazoline (34.3 mg, 50% yield over 3 steps, R_F = 0.52 in 7:1 CH_2Cl_2/MeOH) as a pale yellow semisolid. Optical rotation matched the reported value.[57]



Bisoxazoline 480. Bisoxazoline **480** was synthesized according to a modified procedure of Butula and Karlovic.[58] To a solution of 2-amino-2-methyl-1-proapanol (702 μl, 7.36

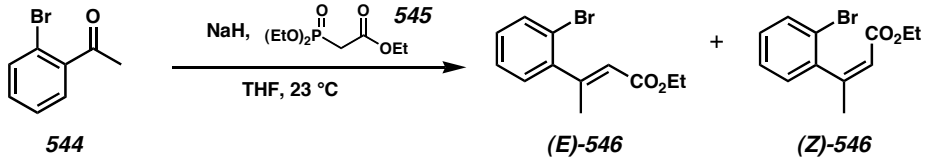
mmol) in 3.68 mL toluene at 23 °C was added diethyl oxalate (500 μl, 3.68 mmol). The mixture was heated to 110 °C and stirred 40 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred 1 h. The white diamide that precipitated (802 mg, 94% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (3.14 g, 13.5 mmol) in 13.5 mL toluene at 60 °C was added $SOCl_2$ (6.14 mL). The resulting mixture was maintained at 60 °C for 30 min, then heated to 100 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and partitioned between EtOAc (150 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

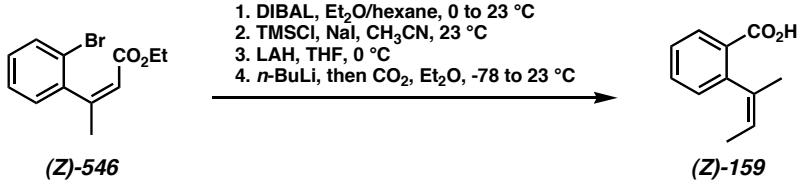
A suspension of the bis alkyl chloride (assume 13.5 mmol) in methanolic KOH (27.0 mL, 1.0 M, 27.0 mmol) was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 90 min, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (3:1 hexanes/acetone eluent) to provide the bisoxazoline (2.30 g, 87% over 2 steps, R_F = 0.32 in 2:1 hexanes/acetone) as a white solid. **Bisoxazoline 480**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (s, 4H), 1.35 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

153.5, 80.0, 68.7, 28.3; IR (film) 2967, 1613, 1103, 949 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{10}H_{16}N_2O_2]^+$: 196.1212, found 196.1216.

5.7.2.2 Synthesis of Carboxylic Acid Substrates



Esters (*E*)-546 and (*Z*)-546. To a suspension of NaH (1.35 g, 60% dispersion in mineral oil, 33.7 mmol) in 36.0 mL THF at 23 °C (kept at that temperature with an external water bath) was added triethyl phosphonoacetate (6.61 mL, 33.3 mmol) dropwise. After stirring for 30 min, the solution was cooled to 0 °C, and a solution of 2-bromoacetophenone (3.00 mL, 22.2 mmol) in 53.0 mL THF was added. The resulting mixture was maintained at 0 °C for 3 h, then allowed to warm to 23 °C and stirred 8 h. The reaction was then quenched at 0 °C with saturated $NaHCO_3$ (100 mL) and extracted with Et_2O (3 x 125 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (14:1 → 4:1 hexanes/Et_2O eluent) afforded the pure olefin isomers of the α,β-unsaturated ester[59] (*E* isomer: 3.55 g, 59% yield, R_F = 0.65 in 4:1 hexanes/EtOAc; *Z* isomer: 1.92 g, 32% yield, R_F = 0.58 in 4:1 hexanes/EtOAc) as colorless oils.



Carboxylic acid (*Z*)-159. To a solution of the (*Z*)-unsaturated ester (1.92 g, 7.13 mmol) in 16.1 mL Et_2O at 0 °C was added DIBAL (14.2 mL, 1.0 M in hexane, 14.2 mmol)

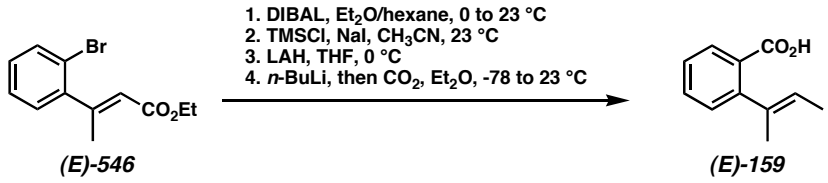
dropwise over 10 min. The reaction was allowed to warm to 23 °C and stirred for 90 min. The mixture was then quenched at 0 °C with brine (20 mL) and diluted with 3 N HCl and aqueous sodium potassium tartrate (10%) until the aqueous phase was clear. The solution was then extracted with Et_2O (3 x 100 mL), and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol (1.59 g, 98% yield, R_F = 0.18 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the allylic alcohol (1.59 g, 7.00 mmol) in 14.0 mL CH_3CN at 23 °C in the dark was added NaI (2.62 g, 17.5 mmol), then TMSCl (1.78 mL, 14.0 mmol). The reaction was stirred at 23 °C for 30 min, and then it was diluted with 150 mL EtOAc and washed sequentially with H_2O (50 mL), 10% aq. sodium thiosulfate (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The allylic iodide (R_F = 0.79 in 4:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a suspension of LAH (1.33 g, 35.0 mmol) in 40 mL THF at 0 °C was added a solution of the crude allylic iodide (assume 7.00 mmol) in 20 mL THF dropwise over 5 min. The reaction was stirred at 0 °C for 30 min. The mixture was then quenched by sequential addition of 1.33 mL H_2O, 1.33 mL 15% aq. NaOH, and 4.00 mL H_2O. The slurry was allowed to warm to room temperature and was stirred vigorously. Once a white precipitate had fully formed (~30 min), the suspension was suction-filtered through a pad of celite (5 x 3 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/CH_2Cl_2 eluent) to provide

the bromoarene (986 mg, 67% yield over 2 steps, R_F = 0.80 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the bromoarene (986 mg, 4.67 mmol) in 46.7 mL THF at –78 °C was added *n*-BuLi (2.14 mL, 2.4 M in hexane, 5.14 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (40 mL) and extracted with Et_2O (3 x 75 mL). The organic layers were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/acetone eluent) afforded carboxylic acid **(*Z*)-159**[3] (671 mg, 82% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a white solid.



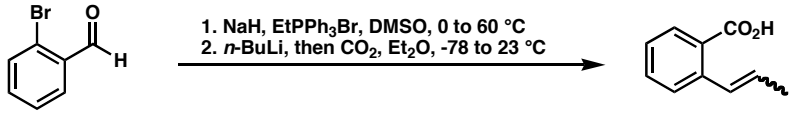
Carboxylic acid (*E*)-159. To a solution of the (*E*)-unsaturated ester (2.35 g, 8.73 mmol) in 19.8 mL Et_2O at 0 °C was added DIBAL (17.5 mL, 1.0 M in hexane, 17.5 mmol) dropwise over 10 min. The reaction was allowed to warm to 23 °C and stirred for 90 min. The mixture was then quenched at 0 °C with brine (20 mL) and diluted with 3 N HCl and aqueous sodium potassium tartrate (10%) until the aqueous phase was clear. The solution was then extracted with Et_2O (3 x 100 mL), and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol (1.98 g, 99% yield, R_F = 0.17 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the allylic alcohol (2.00 g, 8.81 mmol) in 17.6 mL CH_3CN at 23 °C in the dark was added NaI (3.30 g, 22.0 mmol), then TMSCl (2.23 mL, 17.6 mmol). The reaction was stirred at 23 °C for 30 min, and then it was diluted with 150 mL EtOAc and washed sequentially with H_2O (50 mL), 10% aq. sodium thiosulfate (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The allylic iodide (R_F = 0.76 in 4:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a suspension of LAH (1.67 g, 44.1 mmol) in 50 mL THF at 0 °C was added a solution of the crude allylic iodide (assume 8.81 mmol) in 24 mL THF dropwise over 5 min. The reaction was stirred at 0 °C for 30 min. The mixture was then quenched by sequential addition of 1.67 mL H_2O, 1.67 mL 15% aq. NaOH, and 5.00 mL H_2O. The slurry was allowed to warm to room temperature and was stirred vigorously. Once a white precipitate had fully formed (~30 min), the suspension was suction-filtered through a pad of celite (5 x 3 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/CH_2Cl_2 eluent) to provide the bromoarene (1.39 g, 75% yield over 2 steps, R_F = 0.80 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the bromoarene (1.31 g, 6.21 mmol) in 18.8 mL THF at –78 °C was added *n*-BuLi (3.10 mL, 2.4 M in hexane, 7.45 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (50 mL) and extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in

vacuo. Purification of the residue by flash chromatography (4:1 hexanes/acetone eluent) afforded carboxylic acid **(*E*)-159**[3] (577 mg, 53% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a white solid.

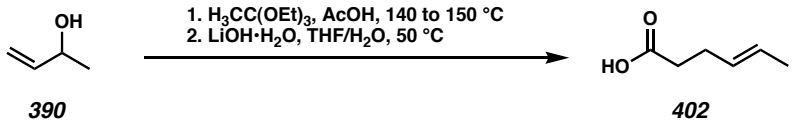


547 ***399***

Carboxylic acid 399. Wittig olefination was performed according to the procedure of Bleckmann and Hanack.[60] Sodium dimsylate was generated by adding NaH (75.2 mg, 60% dispersion in mineral oil, 1.88 mmol) to 940 μl DMSO and heating the mixture at 70 °C for 1 h. The mixture was cooled to 0 °C, and a solution of $EtPPh_3Br$ (668 mg, 1.80 mmol) in 1.00 mL DMSO was added dropwise. The red mixture was allowed to warm to 23 °C and stirred 20 min. A solution of 2-bromobenzaldehyde (200 μl, 1.71 mmol) in 950 μl DMSO was added, and the reaction was heated to 60 °C. After 2.5 h, the mixture was cooled to room temperature, poured into ice water (50 mL), and extracted with hexanes (3 x 50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (100% hexanes eluent) to afford the olefin[61] (153 mg, 45% yield, R_F = 0.61 in 100% hexanes) as a mix of geometrical isomers.

To a solution of the bromoarene (153 mg, 0.776 mmol) in 7.76 mL THF at –78 °C was added *n*-BuLi (342 μl, 2.5 M in hexane, 0.854 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (30 mL) and extracted with Et_2O (3 x 50 mL). The organic layers

were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 → 3:1 hexanes/acetone eluent) afforded carboxylic acid **399**[62] (101 mg, 80% yield, R_F = 0.10 in 4:1 hexanes/EtOAc) as a white solid.

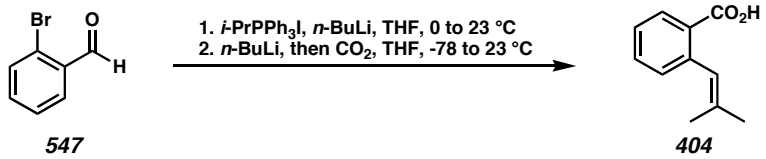


390 *402*

Carboxylic acid 402. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 3-buten-2-ol (2.00 mL, 23.1 mmol), triethyl orthoacetate (6.36 mL, 34.7 mmol), and AcOH (52.3 μl, 0.924 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 200 mL 1 M $KHSO_4$ and 200 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (29:1 hexanes/Et_2O eluent) to afford the ester (1.72 g, 52% yield, R_F = 0.32 in 19:1 hexanes/Et_2O) as a colorless oil.

To a solution of the ester (364 mg, 2.56 mmol) in 6.4 mL THF and 6.4 mL H_2O at 23 °C was added $LiOH•H_2O$ (537 mg, 12.8 mmol). The reaction was heated to 50 °C and stirred vigorously. After 4 h, the mixture was cooled to room temperature, and the THF was removed by rotary evaporation. The aqueous residue was acidified at 0 °C with 2 N HCl and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed

with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to provide carboxylic acid **402**[64] (232 mg, 79% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a colorless oil.



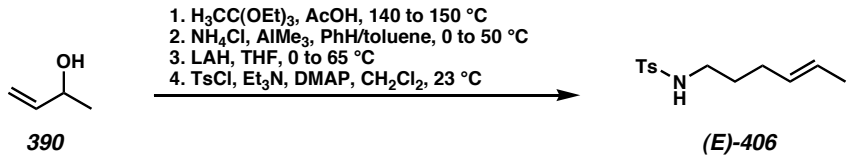
547 *404*

Carboxylic acid 404. To a suspension of *i*-$PrPPh_3I$ (389 mg, 0.900 mmol) in 1.29 mL THF at 0 °C was added *n*-BuLi (360 μl, 2.5 M in hexane, 0.900 mmol) dropwise. The dark red mixture was allowed to warm to 23 °C and stirred for 15 min. The mixture was then cooled to 0 °C, and a solution of 2-bromobenzaldehyde (100 μl, 0.857 mmol) in 429 μl THF was added. The resulting orange mixture was allowed to warm to 23 °C and stirred overnight (8 h). The mixture was then poured into 100 mL pentane with ~3 g celite, and the suspension was stirred 15 min. It was then filtered (pentane eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to afford the olefin[65] (138 mg, 76% yield, R_F = 0.78 in 9:1 hexanes/EtOAc), which was carried on to the next reaction.

To a solution of the bromoarene (138 mg, 0.654 mmol) in 6.54 mL THF at –78 °C was added *n*-BuLi (262 μl, 2.5 M in hexane, 0.654 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (30 mL) and extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/acetone eluent)

afforded carboxylic acid **404**[66] (94.1 mg, 82% yield, R_F = 0.17 in 4:1 hexanes/EtOAc) as a white solid.

5.7.2.3 Synthesis of Amine Substrates



390 *(E)-406*

Tosylamide (*E*)-406. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 3-buten-2-ol (2.00 mL, 23.1 mmol), triethyl orthoacetate (6.36 mL, 34.7 mmol), and AcOH (52.3 μl, 0.924 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 200 mL 1 M $KHSO_4$ and 200 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (29:1 hexanes/Et_2O eluent) to afford the ester (1.72 g, 52% yield, R_F = 0.32 in 19:1 hexanes/Et_2O) as a colorless oil.

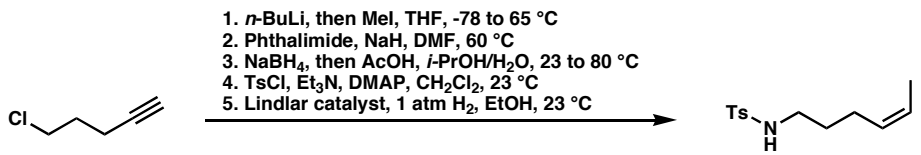
Conversion of the ester to a primary amide was performed according to the procedure of Levin et al.[67] To a suspension of NH_4Cl (1.67 g, 31.2 mmol) in 31.2 mL PhH at 0 °C was added $AlMe_3$ (15.6 mL, 2.0 M in toluene, 31.2 mmol) dropwise over 10 min. The mixture was allowed to warm to 23 °C and stirred for 90 min. Gas evolution was observed during this time. This solution was then added via cannula to a solution of the ester (1.48 g, 10.4 mmol) in 104 mL PhH at 23 °C. The resulting mixture was heated to 50 °C and stirred. After 16 h, the mixture was cooled to room temperature and quenched with 0.5 N HCl (100 mL). The mixture was extracted with EtOAc (3 x 150

mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The amide[64] (R_F = 0.05 in 4:1 hexanes/EtOAc) was carried on without purification.

To a solution of the amide (assume 10.4 mmol) in 52.0 mL THF at 0 °C was added LAH (1.18 g, 31.2 mmol) portionwise slowly. The reaction was heated to 70 °C and stirred for 7 h. The mixture was then cooled to 0 °C and quenched by sequential addition of 1.18 mL H_2O, 1.18 mL 15% NaOH, and 3.54 mL H_2O. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The product amine[64] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 10.4 mmol) in 52.0 mL CH_2Cl_2 at 23 °C was added Et_3N (2.90 mL, 20.8 mmol), TsCl (2.38 g, 12.5 mmol), and DMAP (63.5 mg, 0.520 mmol), sequentially. The reaction was stirred at 23 °C for 8 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/Et_2O eluent) to afford tosylamide **(*E*)-406** (1.16 g, 44% yield over 3 steps, R_F = 0.23 in 4:1 hexanes/EtOAc) as an orange oil. **Tosylamide (*E*)-406**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.43-5.22 (comp m, 2H), 4.56 (br s, 1H), 2.92 (app.q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.95 (app.q, *J* = 7.5 Hz, 2H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.53 (app.quint, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2,

129.9, 129.9, 127.3, 126.4, 42.8, 29.7, 29.4, 21.7, 18.0; IR (film) 3284, 1326, 1160 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{13}H_{20}O_2NS]^+$: 254.1215, found 254.1202.



548 ***(Z)-406***

Tosylamide (*Z*)-406. The first three steps of this synthetic sequence were performed according to a modified procedure of Li and Marks.[68] To a solution of 5-chloro-1-pentyne (2.00 mL, 18.9 mmol) in 18.9 mL THF at –78 °C was added *n*-BuLi (7.92 mL, 2.5 M in hexane, 19.8 mmol) dropwise over 10 min. The reaction was stirred for 1 h, at which point MeI (1.23 mL, 19.8 mmol) was added dropwise. The reaction was allowed to warm to 23 °C, then heated to 65 °C. After 1 h at 65 °C, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl (75 mL), and extracted with Et_2O (3 x 75 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude chloride was carried to the next reaction without purification.

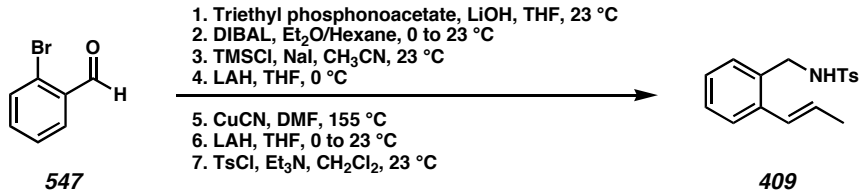
To a solution of phthalimide (1.39 g, 9.45 mmol) in 12.3 mL DMF at 0 °C was added NaH (378 mg, 60% dispersion in mineral oil, 9.45 mmol). The mixture was stirred at 0 °C for 10 min and at 23 °C for 1 h. The chloride (assume 18.9 mmol) was then added to the reaction mixture, and the reaction was heated to 60 °C and stirred overnight (10 h). The mixture was then cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were washed with brine (75 mL), dried over

Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided the alkylated phthalimide (1.63 g, 76% yield, R_F = 0.63 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the phthalimide (1.63 g, 7.17 mmol) in 61.5 mL *i*-PrOH and 10.2 mL H_2O at 23 °C was added $NaBH_4$ (1.36 g, 35.9 mmol). The resulting mixture was stirred at 23 °C for 24 h. AcOH (7.50 mL, 131 mmol) was then added slowly, and the mixture was heated to 80 °C. After 3.5 h, the mixture was cooled to 0 °C and quenched with 1 N HCl (25 mL). After stirring at room temperature for 30 min, the *i*-PrOH was removed by rotary evaporation, and the residue was partitioned between Et_2O (100 mL) and 1 N HCl (50 mL). The organic layer was extracted with 1 N HCl (2 x 25 mL). The combined aqueous phases were basified at 0 °C with KOH pellets (pH > 13), and then extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, dried over K_2CO_3, and concentrated in vacuo. The free amine[68] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 7.17 mmol) in 36.0 mL CH_2Cl_2 at 23 °C was added Et_3N (1.99 mL, 14.3 mmol), TsCl (1.64 g, 8.60 mmol), and DMAP (43.9 mg, 0.359 mmol), sequentially. The reaction was stirred at 23 °C for 10 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 75 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 → 2:1 hexanes/EtOAc eluent) to afford the tosylamide (1.24 g, 69% yield over 2 steps, R_F = 0.42 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkyne (863 mg, 3.43 mmol) in 17.2 EtOH at 23 °C was added Lindlar catalyst (34.3 mg, 5% $Pd/CaCO_3$ with lead poison). The mixture was put under 1 atm H_2 and stirred vigorously. After 75 min, the mixture was filtered through a plug of celite (1 x 5 cm, EtOAc eluent), and the filtrate was concentrated to an oil. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) afforded *cis*-tosylamide **(*Z*)-406** (834 mg, 96% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless oil. **Tosylamide (*Z*)-406**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 5.50-5.35 (m, 1H), 5.33-5.21 (m, 1H), 4.60 (br s, 1H), 2.94 (app.q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.02 (app.q, *J* = 7.5 Hz, 2H), 1.56-1.52 (m, 3H), 1.52 (app.quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 129.1, 127.3, 125.4, 43.1, 29.5, 24.1, 21.7, 12.9; IR (film) 3283, 1325, 1160 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{13}H_{20}O_2NS]^+$: 254.1215, found 254.1217.



547 ***409***

Tosylamide 409. Phosphonoacetate addition was performed according to the procedure of Dyker and Grundt.[59] To a solution of 2-bromobenzaldehyde (100 μl, 0.857 mmol) and triethyl phosphonoacetate (179 ml, 0.900 mmol) in 1.07 mL THF at 23 °C was added LiOH (22.6 mg, 0.943 mmol). The reaction mixture was stirred for 1 h, at which point it was partitioned between 50 mL Et_2O and 30 mL saturated $NaHCO_3$. The aqueous phase was extracted with Et_2O (30 mL), and the organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified

by flash chromatography (19:1 hexanes/EtOAc eluent) to provide the *trans*-(α,β)-unsaturated ester[59] (180 mg, 82% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the ester (1.16 g, 4.55 mmol) in 10.3 mL Et_2O at 0 °C was added DIBAL (9.09 mL, 1.0 M in hexane, 9.09 mmol) dropwise over 5 min. The reaction was allowed to warm to 23 °C and stirred. After 90 min, the mixture was cooled to 0 °C, diluted with Et_2O (100 mL), and quenched with 20 mL brine. Aqueous sodium potassium tartrate (10%) and 3 M HCl were added until the layers were clear, and the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The oil was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol[69] (774 mg, 80% yield, R_F = 0.11 in 4:1 hexanes/EtOAc) as a colorless oil, which was carried to the next reaction.

To a solution of the alcohol (744 mg, 3.63 mmol) in 7.26 mL CH_3CN at 23 °C in the dark was added NaI (925 mg, 6.17 mmol), then TMSCl (783 μl, 6.17 mmol) dropwise. The reaction mixture was stirred for 40 min, then quenched with 40 mL H_2O. The mixture was extracted with EtOAc (100 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 40 mL) and then brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.67 in 4:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (689 mg, 18.2 mmol) in 18.2 mL THF at 0 °C was added a solution of the iodide (assume 3.63 mmol) in 12.1 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 690 μl

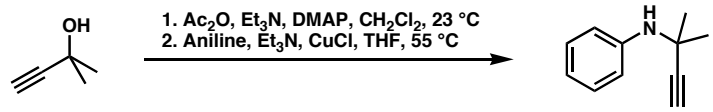
H_2O, 690 μl 15% aqueous NaOH, and 2.07 mL H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (hexanes eluent) provided the (*E*)-alkene[70] (493 mg, 69% yield over 2 steps, R_F = 0.72 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkene (509 mg, 2.58 mmol) in 5.16 mL DMF at 23 °C was added CuCN (347 mg, 3.87 mmol). The heterogeneous mixture was heated to 155 °C and stirred. After 9 h, the mixture was cooled to room temperature and quenched with 720 μl Et_2NH and 30 mL H_2O. The mixture was extracted with Et_2O (5 x 30 mL), and the organic phases were combined, washed with aqueous NaCN (10%, 30 mL) and then brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/Et_2O eluent) to afford the nitrile (316 mg, 86% yield, R_F = 0.41 in 9:1 hexanes/EtOAc) as a colorless oil.

To a suspension of LAH (151 mg, 3.98 mmol) in 11.0 mL THF at 0 °C was added a solution of the nitrile (316 mg, 2.21 mmol) in 7.40 mL THF over 2 min. The resulting mixture was stirred at 0 °C for 15 min, then allowed to warm to 23 °C. After 1 h at 23 °C, the reaction was quenched by adding 151 μl H_2O, 151 μl 15% aqueous NaOH, and 453 mL H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The free amine (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

To a solution of the amine (assume 2.21 mmol) in 11.1 CH_2Cl_2 at 23 °C was added Et_3N (616 μl, 4.42 mmol), then TsCl (505 mg, 2.65 mmol). The reaction was

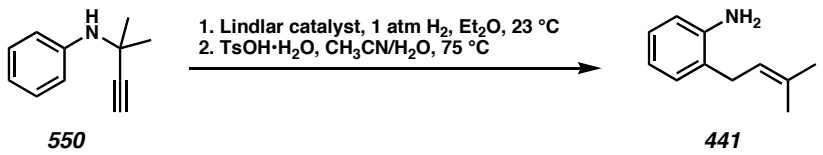
allowed to stir for 11 h. The mixture was quenched with saturated NH_4Cl/H_2O (1:1, 30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided tosylamide **409** (438 mg, 66% yield over 2 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a colorless oil. **Tosylamide 409**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.37-7.29 (comp m, 3H), 7.24-7.19 (m, 1H), 7.14-7.07 (comp m, 2H), 6.37 (d, *J* = 13.8 Hz, 1H), 6.08 (dq, *J* = 6.6, 15.6 Hz, 1H), 4.51 (br s, 1H), 4.13 (d, *J* = 6.0 Hz, 2H), 2.44 (s, 3H), 1.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.5, 136.8, 132.2, 129.9, 129.7, 129.5, 128.7, 127.5, 127.4, 127.3, 126.5, 45.5, 21.7, 18.9; IR (film) 1328, 1160 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{19}NO_2S]^+$: 301.1143, found 301.1136.



549 *550*

Aniline 550. Aniline **550** was synthesized according to the reported procedure.[71] To a solution of 2-methyl-3-butyn-2-ol (3.00 mL, 31.0 mmol) in 31.0 mL CH_2Cl_2 at 23 °C was added Et_3N (4.67 mL, 33.5 mmol), Ac_2O (3.37 mL, 35.7 mmol), and DMAP (174 mg, 1.55 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined, washed with 1 N HCl (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 31.0 mmol) in THF (40.3 mL) at 23 °C under nitrogen was added Et_3N (3.65 mL, 26.2 mmol), aniline (2.17 mL, 23.8 mmol), and CuCl (236 mg, 2.38 mmol), sequentially. The reaction was heated to 55 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 100 mL EtOAc and 75 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (50 mL), then brine (50 mL). The combined aqueous phases were extracted with EtOAc (75 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (15:1 hexanes/EtOAc eluent) to provide aniline **550** (3.41 g, 90% yield, R_F = 0.55 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.

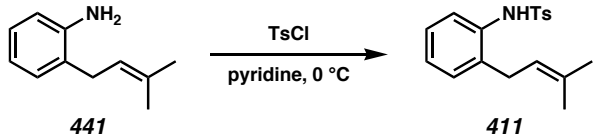


550 ***441***

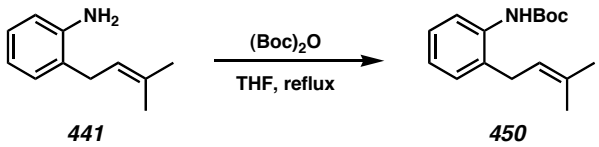
Aniline 441. Free aniline **441** was synthesized according to the procedure of Cooper et al.[72] Aniline **550** (1.02 g, 6.41 mmol) was dissolved in Et_2O (32.1 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 64.1 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 30 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.63 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of alkene (assume 6.41 mmol) in CH_3CN/H_2O (64.1 mL, 9:1) was added $TsOH•H_2O$ (122 mg, 0.641 mmol). The solution was heated to 75 °C and stirred. After 12 h, the mixture was cooled to room temperature, and the CH_3CN was removed by

rotary evaporation. The aqueous residue was extracted with Et_2O (125 mL), and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/EtOAc eluent) afforded aniline **441**[72] (879 mg, 85% yield over 2 steps, R_F = 0.24 in 4:1 hexanes/Et_2O) as a colorless oil.

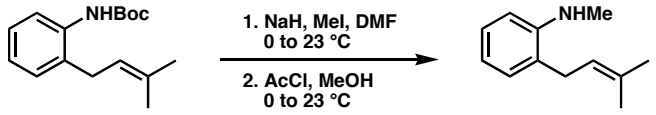


Tosylaniline 411. To a solution of aniline **441** (1.39 g, 8.62 mmol) in 12.3 mL pyridine at 0 °C was added TsCl (1.96 g, 10.3 mmol) portionwise over 2 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 100 mL EtOAc and quenched with 2 N HCl (40 mL). The phases were separated, and the organic phase was washed with 2 N HCl (40 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to provide tosylaniline **411**[73] (1.69 g, 62% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a white semisolid.



Carbamate 450. To a solution of aniline **411** (237 mg, 1.47 mmol) in 1.47 mL THF at 23 °C was added di-*tert*-butyl dicarbonate (354 mg, 1.62 mmol). The reaction mixture was heated to 70 °C. After 2 h, the mixture was cooled to room temperature and

concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and saturated NH_4Cl (30 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to an oil. The residue was purified by flash chromatography (25:1 hexanes/EtOAc eluent) to provide carbamate **450**[74] (374 mg, 97% yield, R_F = 0.41 in 9:1 hexanes/EtOAc) as a colorless oil.

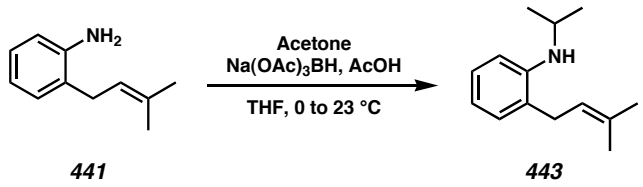


450 ***442***

Aniline 442. To a solution of carbamate **450** (347 mg, 1.33 mmol) in 6.65 mL DMF at 23 °C was added MeI (108 μl, 1.73 mmol). The solution was cooled to 0 °C, and NaH (69.2 mg, 60% dispersion in mineral oil, 1.73 mmol) was added. The reaction mixture was allowed to warm to 23 °C and stirred. After 2 h, the mixture was cooled to 0 °C and quenched with H_2O (25 mL). The mixture was extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with H_2O (2 x 25 mL), then brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (19:1 hexanes/EtOAc eluent) afforded the *N*-methyl carbamate (292 mg, 80% yield, R_F = 0.35 in 9:1 hexanes/EtOAc), which was carried on to the next reaction.

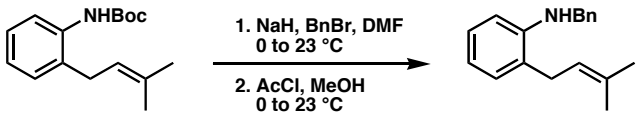
To a solution of the *N*-methyl carbamate (223 mg, 0.810 mmol) in 8.10 mL MeOH at 0 °C was added AcCl (576 μl, 8.10 mmol). The reaction was allowed to warm to 23 °C and stirred for 6 h. The mixture was then quenched with saturated $NaHCO_3$ (30 mL). The methanol was removed by rotary evaporation, and the aqueous residue was extracted with 100 mL EtOAc. The organic phase was washed with brine (40 mL), dried

over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (40:1 hexanes/EtOAc) to provide *N*-methyl aniline **442**[75] (128 mg, 90% yield, R_F = 0.48 in 9:1 hexanes/EtOAc) as a colorless oil.



441 ***443***

Aniline 443. To a solution of aniline **441** (114 mg, 0.707 mmol) in 3.54 mL THF at 0 °C was added acetone (115 μl, 1.56 mmol), AcOH (80.7 μl, 1.41 mmol), and $Na(OAc)_3BH$ (449 mg, 2.12 mmol), sequentially. The reaction mixture was allowed to warm to 23 °C and stirred. After 23 h, the mixture was cooled to 0 °C, quenched with 30 mL H_2O, and extracted with EtOAc (60 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (40:1 hexanes/EtOAc eluent) afforded *N*-isopropyl aniline **443** (128 mg, 89% yield, R_F = 0.53 in 9:1 hexanes/EtOAc) as a colorless oil. **Aniline 443**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (app.t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.65 (app.t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 5.24-5.18 (m, 1H), 3.64 (septet, *J* = 6.3 Hz, 1H), 3.62 (br s, 1H), 3.20 (d, *J* = 6.9 Hz, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.4, 129.7, 127.5, 125.6, 122.5, 116.8, 111.1, 44.2, 31.5, 25.9, 23.3, 18.1; IR (film) 2967, 1604, 1510, 745 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{21}N]^+$: 203.1674, found 203.1680.

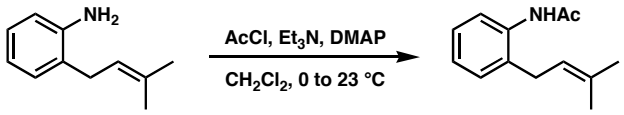


450 *444*

Aniline 444. To a solution of carbamate **450** (317 mg, 1.21 mmol) in 6.05 mL DMF at 23 °C was added BnBr (187 μl, 1.57 mmol). The solution was cooled to 0 °C, and NaH (62.8 mg, 60% dispersion in mineral oil, 1.57 mmol) was added. The reaction mixture was allowed to warm to 23 °C and was stirred. After 2 h, the mixture was cooled to 0 °C and quenched with H_2O (25 mL). The mixture was extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with H_2O (2 x 25 mL), then brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) afforded the *N*-benzyl carbamate (356 mg, 84% yield, R_F = 0.45 in 4:1 hexanes/Et_2O), which was carried on to the next reaction.

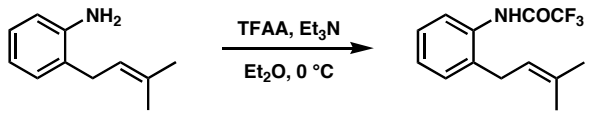
To a solution of the *N*-benzyl carbamate (356 mg, 1.01 mmol) in 10.1 mL MeOH at 0 °C was added AcCl (718 μl, 10.1 mmol). The reaction was allowed to warm to 23 °C and stirred for 8 h. The mixture was then quenched with saturated $NaHCO_3$ (40 mL). The methanol was removed by rotary evaporation, and the aqueous residue was extracted with 100 mL EtOAc. The organic phase was washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (30:1 hexanes/EtOAc eluent) to provide *N*-benzyl aniline **444** (218 mg, 86% yield, R_F = 0.56 in 9:1 hexanes/EtOAc) as a colorless oil. **Aniline 444**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.14 (app.t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.72 (app.t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.27-5.21 (m, 1H), 4.34 (s, 2H), 4.11 (br s, 1H), 3.25 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4,

139.6, 133.9, 129.5, 128.8, 127.9, 127.6, 127.5, 125.7, 122.1, 117.6, 110.7, 48.6, 31.4, 25.9, 17.9; IR (film) 1509, 747 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{18}H_{21}N]^+$: 251.1674, found 251.1675.



441 *445*

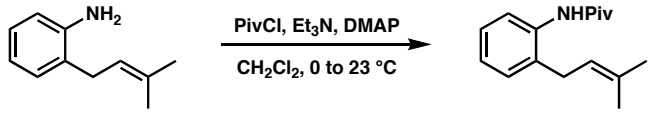
Acetanilide 445. To a solution of aniline **441** (88.2 mg, 0.547 mmol) in 2.24 mL CH_2Cl_2 at 0 °C was added Et_3N (229 μl, 1.64 mmol), DMAP (3.3 mg, 0.0274 mmol), and AcCl (46.6 μl, 0.656 mmol), sequentially. The reaction mixture was allowed to warm to 23 °C. After 30 min, the mixture was quenched with saturated NH_4Cl (25 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic phases were combined and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide acetanilide **445**[76] (88.9 mg, 80% yield, R_F = 0.07 in 4:1 hexanes/EtOAc) as a white solid.



441 *447*

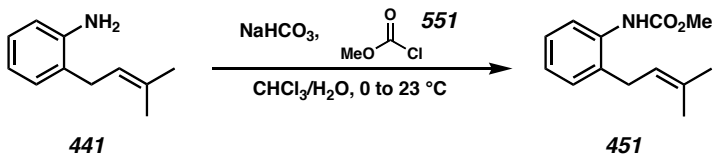
Trifluoroacetamide 447. To a solution of aniline **441** (111 mg, 0.688 mmol) in 3.44 mL Et_2O at 0 °C was added Et_3N (287 μl, 2.06 mmol), then trifluoroacetic anhydride (126 μl, 0.894 mmol). The reaction was stirred at 0 °C. After 1 h, the mixture was quenched with saturated NH_4Cl (25 mL) and extracted with Et_2O (2 x 35 mL). The organic phases were

combined, washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (14:1 hexanes/Et_2O eluent) to provide trifluoroacetamide **447**[76] (152 mg, 86% yield, R_F = 0.48 in 4:1 hexanes/Et_2O) as a white solid.

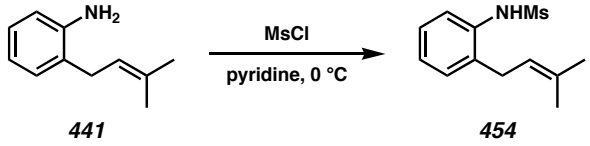


441 *449*

Amide 449. To a solution of aniline **441** (90.8 mg, 0.563 mmol) in 2.82 mL CH_2Cl_2 at 0 °C was added Et_3N (236 µl, 1.69 mmol), DMAP (3.4 mg, 0.0282 mmol), and trimethylacetyl chloride (83.3 µl, 0.676 mmol), sequentially. The mixture was allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with saturated NH_4Cl/H_2O (30 mL, 1:1) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined and washed with saturated $NaHCO_3$, then brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided amide **449** (119 mg, 86% yield, R_F = 0.10 in 1:1 hexanes/CH_2Cl_2) as a white solid. **Amide 449**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.51 (br s, 1H), 7.23 (app.t, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.05 (app.t, *J* = 7.5 Hz, 1H), 5.24-5.18 (m, 1H), 3.33 (d, *J* = 6.3 Hz, 2H), 1.77 (app.s, 6H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 136.5, 135.3, 131.6, 129.9, 127.3, 124.7, 122.8, 122.2, 39.8, 31.7, 27.7, 25.8, 18.6; IR (film) 1655, 1520, 1450 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{23}NO]^+$: 245.1780, found 245.1777.

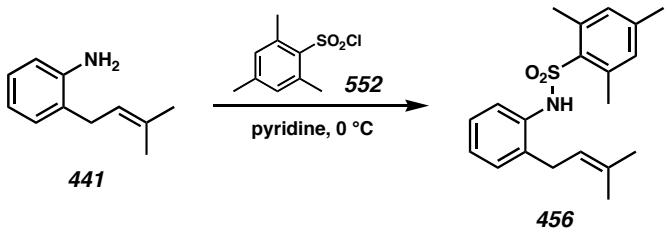


Carbamate 451. To a solution of aniline **441** (105 mg, 0.651 mmol) in 1.30 mL $CHCl_3$ at 23 °C was added 2.60 mL aqueous saturated $NaHCO_3$. The mixture was cooled to 0 °C, and methyl chloroformate (121 μl, 1.56 mmol) was added. The reaction was allowed to warm to 23 °C and was stirred. After 1.5 h, the mixture was partitioned between 50 mL CH_2Cl_2 and 30 mL saturated $NaHCO_3$. The organic layer was washed with water (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (15:1 hexanes/EtOAc eluent) to afford methyl carbamate **451** (143 mg, 99% yield, R_F = 0.45 in 2:1 hexanes/Et_2O) as a colorless oil. **Carbamate 451**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.23 (app.t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.04 (app.t, *J* = 7.2 Hz, 1H), 6.65 (br s, 1H), 5.22-5.16 (m, 1H), 3.77 (s, 3H), 3.30 (d, *J* = 6.9 Hz, 2H), 1.80 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 136.3, 134.4, 131.0, 129.8, 127.3, 124.3, 121.8, 52.5, 31.7, 25.9, 18.0; IR (film) 1740, 1524, 1454, 1226 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{17}NO_2]^+$: 219.1259, found 219.1251.



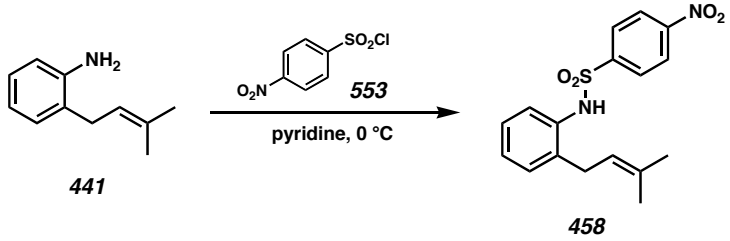
Sulfonamide 454. To a solution of aniline **441** (100 mg, 0.620 mmol) in 2.07 mL pyridine at 0 °C was added MsCl (57.6 μl, 0.744 mmol) dropwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 40 mL

EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide sulfonamide **454** (141 mg, 95% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a white semisolid. **Sulfonamide 454**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 1H), 7.27-7.20 (comp m, 2H), 7.14 (app.t, *J* = 7.2 Hz, 1H), 6.48 (br s, 1H), 5.21-5.14 (m, 1H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.99 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 135.3, 132.8, 130.7, 127.9, 126.0, 122.1, 121.4, 39.9, 31.8, 25.9, 18.1; IR (film) 1326, 1154 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{17}O_2NS]^+$: 239.0980, found 239.0986.



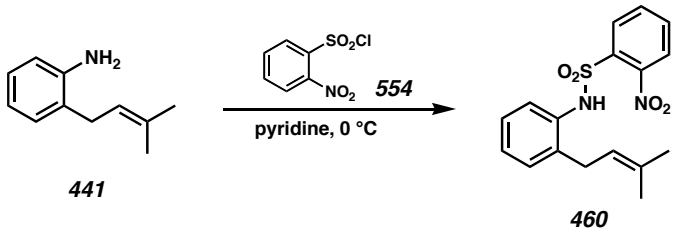
Sulfonamide 456. To a solution of aniline **441** (112 mg, 0.695 mmol) in 2.32 mL pyridine at 0 °C was added 2-mesitylenesulfonyl chloride (182 mg, 0.834 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (12:1 hexanes/EtOAc eluent)

to provide sulfonamide **456** (204 mg, 85% yield, R_F = 0.34 in 4:1 hexanes/acetone) as a white solid. **Sulfonamide 456**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.11 (m, 1H), 7.07-7.01 (comp m, 2H), 6..94 (s, 2H), 6.87-6.84 (m, 1H), 6.63 (br s, 1H), 5.14-5.08 (m, 1H), 3.27 (d, *J* = 6.9 Hz, 2H), 2.56 (s, 6H), 2.30 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 139.4, 135.5, 135.2, 134.7, 133.8, 132.3, 130.3, 127.2, 125.6, 122.5, 121.7, 31.5, 25.9, 23.2, 21.2, 18.2; IR (film) 1330, 1154 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{25}NO_2S]^+$: 343.1606, found 343.1596.



Sulfonamide 458. To a solution of aniline **441** (124 mg, 0.769 mmol) in 2.56 mL pyridine at 0 °C was added 4-nitrobenzenesulfonyl chloride (228 mg, 0.923 mmol) portionwise over 1 min. The dark red mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide sulfonamide **458** (241 mg, 90% yield, R_F = 0.31 in 4:1 hexanes/EtOAc) as an orange oil. **Sulfonamide 458**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.22 (app.t, *J* = 7.8 Hz, 1H), 7.14 (app.t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.72 (br s, 1H), 4.99-4.93 (m, 1H), 2.96 (d, *J* = 7.2 Hz,

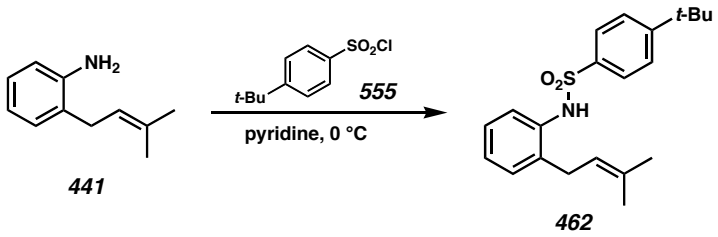
2H), 1.74 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 145.5, 135.4, 134.2, 134.1, 130.6, 128.5, 127.9, 127.0, 124.4, 124.1, 121.2, 31.5, 25.9, 18.1; IR (film) 1531, 1349, 1167 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{18}N_2O_4S]^+$: 346.0987, found 346.0971.



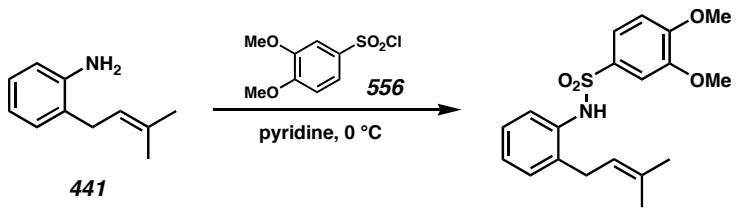
441 *460*

Sulfonamide 460. To a solution of aniline **441** (130 mg, 0.806 mmol) in 2.69 mL pyridine at 0 °C was added 2-nitrobenzenesulfonyl chloride (214 mg, 0.967 mmol) portionwise over 1 min. The dark red mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide sulfonamide **460** (215 mg, 77% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as an orange oil. **Sulfonamide 460**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.73 (app.t, *J* = 7.8 Hz, 1H), 7.64 (app.t, *J* = 7.8 Hz, 1H), 7.25-7.20 (comp m, 2H), 7.18-7.11 (comp m, 2H), 7.16 (br s, 1H), 5.07-5.01 (m, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 136.3, 134.8, 133.8, 133.7, 132.7, 131.3, 130.1, 127.0, 126.9, 125.3, 124.8, 121.0, 30.3, 25.7, 17.9; IR (film)

1541, 1169 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{18}N_2O_4S]^+$: 346.0987, found 346.0983.

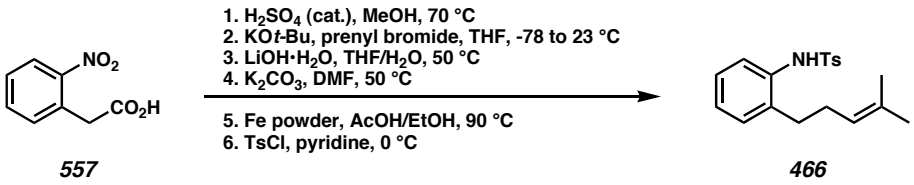


Sulfonamide 462. To a solution of aniline **441** (101 mg, 0.626 mmol) in 2.09 mL pyridine at 0 °C was added 4-*tert*-butylbenzenesulfonyl chloride (175 mg, 0.751 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide sulfonamide **462** (203 mg, 91% yield, R_F = 0.39 in 4:1 hexanes/acetone) as a white solid. **Sulfonamide 462**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.21-7.16 (m, 1H), 7.11-7.05 (comp m, 2H), 6.55 (br s, 1H), 5.00-4.95 (m, 1H), 2.96 (d, *J* = 6.9 Hz, 2H), 1.73 (s, 3H), 1.68 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 137.0, 135.3, 135.0, 133.5, 130.1, 127.5, 127.1, 126.1, 126.0, 123.7, 121.4, 35.3, 31.3, 31.2, 25.9, 18.1; IR (film) 2966, 1166 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{27}NO_2S]^+$: 357.1762, found 357.1750.



441 464

Sulfonamide 464. To a solution of aniline **441** (108 mg, 0.670 mmol) in 2.23 mL pyridine at 0 °C was added 3,4-dimethoxybenzenesulfonyl chloride (190 mg, 0.804 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/Et_2O eluent) to provide sulfonamide **464** (231 mg, 95% yield, R_F = 0.11 in 4:1 hexanes/EtOAc) as a white solid. **Sulfonamide 464**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.20 (app.t, *J* = 7.2 Hz, 1H), 7.10 (app.t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.51 (br s, 1H), 5.00-4.94 (m, 1H), 3.90 (s, 3H), 3.70 (s, 3H), 2.91 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 148.9, 135.4, 135.0, 134.3, 131.5, 130.1, 127.5, 126.3, 124.5, 121.4, 121.0, 110.6, 109.7, 56.3, 56.2, 31.3, 25.9, 18.0; IR (film) 1509, 1263, 1156 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{23}NO_4S]^+$: 361.1348, found 361.1348.



557 *466*

Tosylaniline 466. Methyl 2-nitrophenylacetate was synthesized according to the procedure of Lee et al.[77] To a solution of 2-nitrophenylacetic acid (200 mg, 1.10 mmol) in 1.10 mL MeOH at 23 °C was added 1 drop (pipet) conc. H_2SO_4. The solution was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between 75 mL EtOAc and 50 mL saturated $NaHCO_3$. The organic layer was washed with H_2O (35 mL) and then brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo. The oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford the methyl ester (181 mg, 84% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless oil.

The monoalkylation of methyl 2-nitrophenylacetate was performed according to the procedure of Prasad et al.[78] To a solution of the methyl ester (369 mg, 1.89 mmol) in 28.2 mL THF at 23 °C was added prenyl bromide (266 μl, 2.08 mmol). The solution was cooled to –78 °C, and KO*t*-Bu (233 mg, 2.08 mmol) was added. After 10 min at –78 °C, the mixture was allowed to warm to 23 °C. After 1 h, the mixture was quenched at 0 °C with saturated NH_4Cl (40 mL) and extracted with Et_2O (2 x 60 mL). The organic layers were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide the alkylated ester (480 mg, 96% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

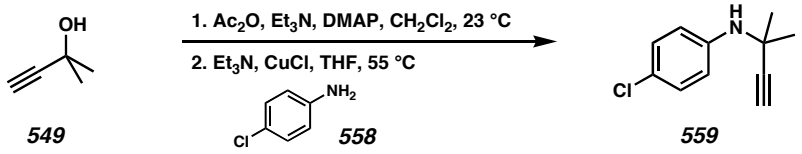
The saponification-decarboxylation sequence was performed according to a modified procedure of Bull et al.[79] To a solution of the ester (480 mg, 1.82 mmol) in THF/H_2O (9.10 mL, 1:1) at 23 °C was added LiOH•H_2O (382 mg, 9.10 mmol). The mixture was heated to 50 °C. After 4 h, the reaction was cooled to room temperature and partitioned between Et_2O (60 mL) and 1 N HCl (30 mL). The aqueous phase was extracted with Et_2O (50 mL), and the organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The product acid (R_F = 0.00 in 9:1 hexanes/EtOAc) was carried on directly to the next reaction.

To a solution of the acid (assume 1.82 mmol) in 5.52 mL DMF at 23 °C was added K_2CO_3 (252 mg, 1.82 mmol). The mixture was heated to 50 °C and stirred for 2 h. The mixture was then cooled to room temperature and partitioned between 50 mL Et_2O and 40 mL 0.5 N HCl. The aqueous phase was extracted with Et_2O (30 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (14:1 hexanes/Et_2O eluent) to afford the decarboxylated product (257 mg, 69% yield over 2 steps, R_F = 0.48 in 9:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

To a solution of the nitroarene (274 mg, 1.33 mmol) in EtOH/AcOH (35.0 mL, 1:1) at 80 °C was added iron powder (670 mg, 12.0 mmol). The resulting slurry was heated to 90 °C. After 1 h, the mixture was cooled to 40 °C, and solid Na_2CO_3 was added slowly to neutralize the reaction. The mixture was then partitioned between EtOAc (100 mL) and H_2O (50 mL), and the aqueous phase was extracted with EtOAc (50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to

provide the aniline (181 mg, 77% yield, R_F = 0.26 in 9:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the aniline (181 mg, 1.03 mmol) in 3.43 mL pyridine at 0 °C was added TsCl (236 mg, 1.24 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide tosylaniline **466** (266 mg, 78% yield, R_F = 0.15 in 9:1 hexanes/EtOAc) as a white solid. **Tosylaniline 466**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 6.9 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.17-7.07 (comp m, 3H), 6.56 (br s, 1H), 5.10-5.04 (m, 1H), 2.38 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.10 (app.q, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 137.0, 135.6, 134.4, 134.3, 130.2, 129.8, 127.3, 127.2, 126.5, 124.7, 123.1, 31.2, 28.8, 25.9, 21.7, 17.8; IR (film) 3276, 1329, 1161 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{19}H_{24}O_2NS]^+$: 330.1528, found 330.1534.

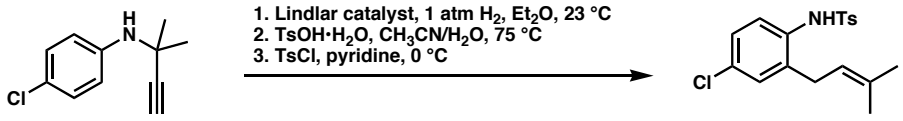


549 *558* *559*

Aniline 559. To a solution of 2-methyl-3-butyn-2-ol (500 μl, 5.16 mmol) in 5.16 mL CH_2Cl_2 at 23 °C was added Et_3N (776 μl, 5.57 mmol), Ac_2O (561 μl, 5.93 mmol), and DMAP (28.9 mg, 0.258 mmol), sequentially. The reaction was stirred at 23 °C overnight

(8 h). The reaction was then poured over saturated NH_4Cl (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 35 mL) and brine (35 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 5.16 mmol) in THF (5.16 mL) at 23 °C under nitrogen was added Et_3N (609 μl, 4.37 mmol), 4-chloroaniline (506 mg, 3.97 mmol), and CuCl (39.3 mg, 0.397 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 75 mL EtOAc and 50 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide aniline **559** (651 mg, 85% yield, R_F = 0.49 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.

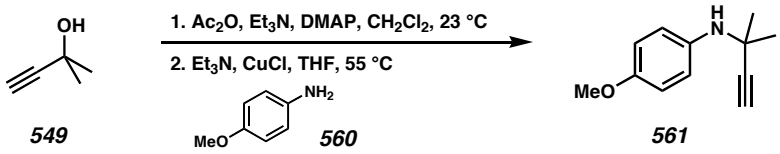


559 ***468***

Tosylaniline 468. Aniline **559** (364 mg, 1.88 mmol) was dissolved in Et_2O (9.40 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 18.8 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 40 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.60 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 1.88 mmol) in CH_3CN/H_2O (18.8 mL, 9:1) was added $TsOH•H_2O$ (35.7 mg, 0.188 mmol). The solution was heated to 75 °C and stirred. After 24 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (75 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) afforded the rearranged aniline[80] (255 mg, 69% yield over 2 steps, R_F = 0.44 in 4:1 hexanes/EtOAc) as a colorless oil.

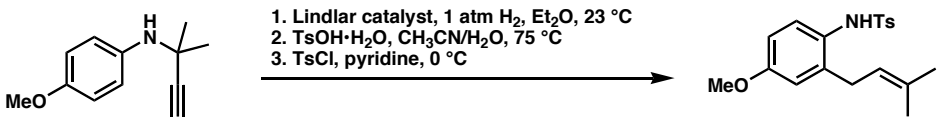
To a solution of the aniline (255 mg, 1.30 mmol) in 4.33 mL pyridine at 0 °C was added TsCl (297 mg, 1.56 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide tosylaniline **468** (363 mg, 80% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless semisolid. **Tosylaniline 468**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.14 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.48 (br s, 1H), 4.96-4.89 (m, 1H), 2.91 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 136.7, 135.8, 135.8, 133.8, 131.5, 130.0, 129.9, 127.5, 127.3, 125.4, 120.5, 31.0, 25.9, 21.8, 18.1; IR (film) 1162 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{18}H_{20}NO_2SCl]^+$: 349.0907, found 349.0903.



549 *560* *561*

Aniline 561. To a solution of 2-methyl-3-butyn-2-ol (500 μl, 5.16 mmol) in 5.16 mL CH_2Cl_2 at 23 °C was added Et_3N (776 μl, 5.57 mmol), Ac_2O (561 μl, 5.93 mmol), and DMAP (28.9 mg, 0.258 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 35 mL) and brine (35 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 5.16 mmol) in THF (5.16 mL) at 23 °C under nitrogen was added Et_3N (609 μl, 4.37 mmol), *p*-anisidine (489 mg, 3.97 mmol), and CuCl (39.3 mg, 0.397 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 75 mL EtOAc and 50 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide aniline **561** (646 mg, 86% yield, R_F = 0.37 in 4:1 hexanes/EtOAc) as an orange oil, which was carried on.



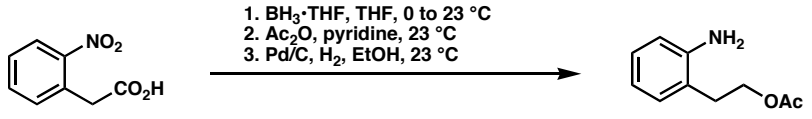
561 ***470***

Tosylaniline 470. Aniline **561** (324 mg, 1.72 mmol) was dissolved in Et_2O (8.56 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 17.1 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 10 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The resulting oil was purified by flash chromatography (5:1 hexanes/EtOAc) to provide the alkene (279 mg, 85% yield, R_F = 0.40 in 4:1 hexanes/acetone), which was carried on directly to the subsequent reaction.

To a solution of the alkene (279 mg, 1.46 mmol) in CH_3CN/H_2O (15.7 mL, 9:1) was added $TsOH•H_2O$ (27.8 mg, 0.146 mmol). The solution was heated to 75 °C and stirred. After 24 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (75 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (5:1 hexanes/EtOAc eluent) afforded the rearranged aniline[80] (233 mg, 84% yield, R_F = 0.58 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of the aniline (233 mg, 1.22 mmol) in 4.07 mL pyridine at 0 °C was added TsCl (278 mg, 1.46 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried

over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide tosylaniline **470** (383 mg, 91% yield, R_F = 0.19 in 4:1 hexanes/acetone) as a yellow oil. **Tosylaniline 470**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.60 (s, 1H), 6.24 (br s, 1H), 4.97-4.90 (m, 1H), 3.76 (s, 3H), 2.85 (d, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 143.8, 137.7, 137.0, 134.7, 129.7, 127.6, 127.5, 127.4, 121.3, 115.7, 111.9, 55.5, 31.1, 25.9, 21.8, 18.0; IR (film) 1496, 1161 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{23}NO_3S]^+$: 345.1399, found 345.1388.



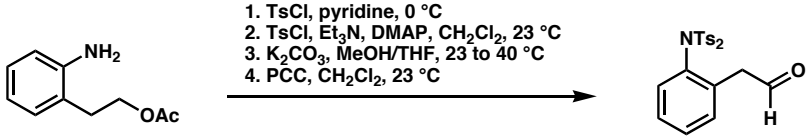
557 ***562***

Aniline 562. Aniline **562** was synthesized according to the procedure of Yamashita et al.[81] To a solution of 2-nitrophenylacetic acid (1.00 g, 5.52 mmol) in 3.25 mL THF at 0 °C was added BH_3•THF (11.0 mL, 1.0 M in THF, 11.0 mmol) dropwise over 3 min. The mixture was allowed to warm to 23 °C and stirred overnight. After 12 h, the reaction was cooled to 0 °C and quenched with H_2O (15 mL). The mixture was partitioned between 100 mL EtOAc and 50 mL saturated $NaHCO_3$. The organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided the alcohol[82] (915 mg, 99% yield, R_F = 0.19 in 2:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of the alcohol (915 mg, 5.47 mmol) in 6.59 mL pyridine at 23 °C was added 6.59 mL Ac_2O. The mixture was stirred for 30 min, and then concentrated to

an oil. The residue was azeotroped with MeOH (3 x 20 mL), then toluene (2 x 20 mL). The residue was then dissolved in 125 mL $CHCl_3$ and washed with 75 mL saturated $NaHCO_3$. The aqueous phase was extracted with 50 mL $CHCl_3$, and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The acetate[83] (1.08 g, 94% yield, R_F = 0.54 in 2:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

To a solution of the acetate (1.08 g, 5.16 mmol) in 51.6 mL EtOH at 23 °C was added Pd/C (108 mg, 10%). The suspension was put under 1 atm H_2 and stirred vigorously for 90 min. The mixture was filtered through a plug of celite (1.5 x 5 cm, EtOAc eluent), and the filtrate was concentrated to an oil. Aniline **562** (R_F = 0.19 in 4:1 hexanes/EtOAc) was carried on directly to the next reaction.



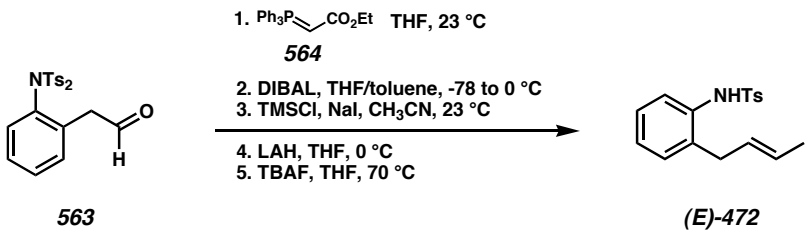
562 ***563***

Aldehyde 563. To a solution of the aniline (assume 5.16 mmol) in 12.9 mL pyridine at 0 °C was added TsCl (1.18 g, 6.19 mmol) portionwise over 2 min. The reaction was stirred for 1 h at 0 °C. The mixture was then diluted with 100 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford the tosylaniline (1.58 g, 92% yield over 2 steps, R_F = 0.34 in 2:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the tosylaniline (1.58 g, 4.74 mmol) in 47.4 mL CH_2Cl_2 at 23 °C was added Et_3N (1.98 mL, 14.2 mmol), TsCl (1.08 g, 5.69 mmol), and DMAP (29.0 mg, 0.237 mmol), sequentially. The reaction was stirred at 23 °C for 45 min, at which point it was diluted with 100 mL CH_2Cl_2 and washed with saturated NH_4Cl/H_2O (1:1, 50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide the bis(tosyl)aniline (2.31 g, 100% yield, R_F = 0.43 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of the bis(tosyl)aniline (213 mg, 0.437 mmol) in THF/MeOH (3.36 mL, 1:1) at 40 °C was added K_2CO_3 (66.5 mg, 0.481 mmol). The reaction was stirred at 40 °C for 1 h, then cooled to room temperature and quenched with saturated $NaHCO_3$ (10 mL). The organic solvents were removed by rotary evaporation, and the aqueous residue was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided the alcohol (189 mg, 97% yield, R_F = 0.14 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a suspension of PCC (535 mg, 2.48 mmol) in 3.30 mL CH_2Cl_2 at 23 °C was added a solution of the alcohol (735 mg, 1.65 mmol) in 3.30 mL CH_2Cl_2 dropwise over 1 min. The reaction was stirred at 23 °C for 1 h. The solution was then diluted with 50 mL Et_2O, and the heterogeneous mixture was filtered through a plug of SiO_2 (1.5 x 10 cm, Et_2O eluent). The filtrate was concentrated in vacuo, and the crude residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide aldehyde **563** (545 mg, 75% yield, R_F = 0.42 in 2:1 hexanes/EtOAc) as a white foam.



563 *(E)-472*

Tosylaniline (*E*)-472. Wittig olefination was performed according to the procedure of Matsumori et al.[84] To a solution of aldehyde **563** (545 mg, 1.23 mmol) in 12.3 mL THF at 23 °C was added (carbethoxymethylene)triphenylphosphorane (557 mg, 1.60 mmol). The reaction was stirred at 23 °C for 12 h, then partitioned between 100 mL Et_2O and 50 mL H_2O. The aqueous phase was extracted with Et_2O (50 mL), and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/Et_2O eluent) to afford the *trans*-α,β-unsaturated ester (412 mg, 65% yield, R_F = 0.48 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

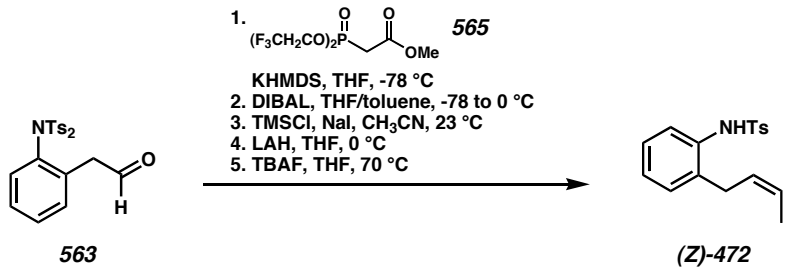
To a solution of the ester (412 mg, 0.802 mmol) in 3.21 mL THF at –78 °C was added DIBAL (1.39 mL, 1.5 M in toluene, 2.09 mmol) dropwise over 3 min. The reaction was stirred for 1 h at –78 °C, then allowed to warm to 0 °C and stirred for an additional 1 h. The reaction mixture was then quenched with 1 N HCl (30 mL) at 0 °C, and it was extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 → 3:2 hexanes/EtOAc eluent) to provide the allylic alcohol (R_F = 0.13 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (assume 0.802 mmol) in 1.61 mL CH_3CN at 23 °C in the dark was added NaI (301 mg, 2.01 mmol), then TMSCl (203 μl, 1.60 mmol) dropwise. The reaction mixture was stirred for 15 min, then quenched with 30 mL H_2O. The mixture was extracted with EtOAc (75 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.55 in 2:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (152 mg, 4.01 mmol) in 3.34 mL THF at 0 °C was added a solution of the iodide (assume 0.802 mmol) in 3.34 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 152 μl H_2O, 152 μl 15% aqueous NaOH, and 456 μl H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided the *E*-alkene (299 mg, 82% yield over 3 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a white solid.

Selective monodesulfonylation was carried out according to the procedure of Yasuhara et al.[85] To a solution of the bis(tosyl)aniline (362 mg, 0.795 mmol) in 7.95 mL THF at 23 °C was added TBAF (1.59 mL, 1.0 M in THF, 1.59 mmol). The reaction was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and 30 mL H_2O was added. The mixture was extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1

hexanes/Et_2O eluent) to provide tosylaniline **(*E*)-472**[86] (213 mg, 89% yield, R_F = 0.26 in 2:1 hexanes/Et_2O) as a white semisolid.



Tosylaniline (*Z*)-472. The Still-modification of the Horner-Wadsworth-Emmons reaction was performed according to the procedure of Gleave and Brickner.[87] To a solution of phosphonate **565** (116 μl, 0.545 mmol) in 3.88 mL THF at –78 °C was added KHMDS (545 μl, 1.0 M in THF, 0.545 mmol). The mixture was stirred for 5 min, and then a solution of aldehyde **563** (230 mg, 0.514 mmol) in 3.88 mL THF was added. The reaction was stirred at –78 °C for 1 h, and then it was quenched with saturated NH_4Cl (30 mL) and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 30 mL), and the combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/Et_2O) to provide the *cis*-α,β-unsaturated ester (183 mg, 71% yield, R_F = 0.54 in 2:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

To a solution of the ester (487 mg, 0.975 mmol) in 3.90 mL THF at –78 °C was added DIBAL (1.69 mL, 1.5 M in toluene, 2.54 mmol) dropwise over 3 min. The reaction was stirred for 1 h at –78 °C, then allowed to warm to 0 °C and stirred for an additional 1 h. The reaction mixture was then quenched with 1 N HCl (40 mL) at 0 °C, and it was extracted with EtOAc (3 x 75 mL). The organic layers were combined,

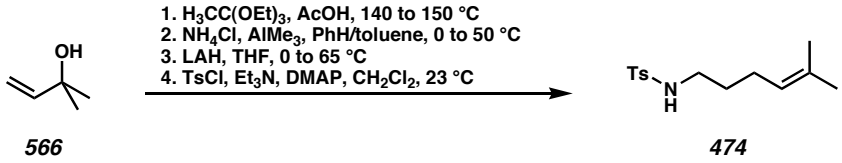
washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 → 3:2 hexanes/EtOAc eluent) to provide the allylic alcohol (R_F = 0.13 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (assume 0.975 mmol) in 1.95 mL CH_3CN at 23 °C in the dark was added NaI (366 mg, 2.44 mmol), then TMSCl (247 μl, 1.95 mmol) dropwise. The reaction mixture was stirred for 15 min, then quenched with 30 mL H_2O. The mixture was extracted with EtOAc (75 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.60 in 2:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (185 mg, 4.88 mmol) in 4.07 mL THF at 0 °C was added a solution of the iodide (assume 0.975 mmol) in 4.07 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 185 μl H_2O, 185 μl 15% aqueous NaOH, and 555 μl H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided the *Z*-alkene (397 mg, 89% yield over 3 steps, R_F = 0.62 in 2:1 hexanes/EtOAc) as a white solid.

Selective monodesulfonylation was carried out according to the procedure of Yasuhara et al.[85] To a solution of the bis(tosyl)aniline (397 mg, 0.871 mmol) in 8.71 mL THF at 23 °C was added TBAF (1.74 mL, 1.0 M in THF, 1.74 mmol). The reaction was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and

30 mL H_2O was added. The mixture was extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/Et_2O eluent) to provide tosylaniline **(*Z*)-472**[86] (244 mg, 93% yield, R_F = 0.26 in 2:1 hexanes/Et_2O) as a white semisolid.



Tosylamide 474. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 2-methyl-3-buten-2-ol (1.00 mL, 9.57 mmol), triethyl orthoacetate (2.64 mL, 14.4 mmol), and AcOH (21.9 μl, 0.383 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 150 mL 1 M $KHSO_4$ and 150 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (75 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to afford the ester (297 mg, 20% yield, R_F = 0.48 in 9:1 hexanes/EtOAc) as a colorless oil.

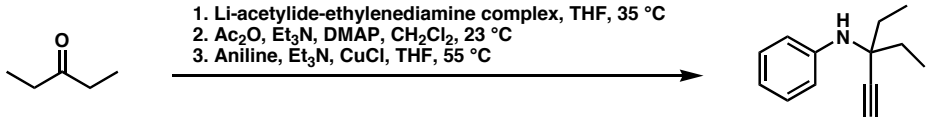
Conversion of the ester to a primary amide was performed according to the procedure of Levin et al.[67] To a suspension of NH_4Cl (266 mg, 4.98 mmol) in 4.98 mL PhH at 0 °C was added $AlMe_3$ (2.49 mL, 2.0 M in toluene, 4.98 mmol) dropwise over 10 min. The mixture was allowed to warm to 23 °C and was stirred for 90 min. Gas

evolution was observed during this time. This solution was then added via cannula to a solution of the ester (259 mg, 1.66 mmol) in 16.6 mL PhH at 23 °C. The resulting mixture was heated to 50 °C and stirred. After 16 h, the mixture was cooled to room temperature and quenched with 0.5 N HCl (50 mL). The mixture was extracted with EtOAc (3 x 60 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The amide (R_F = 0.02 in 4:1 hexanes/EtOAc) was carried on without purification.

To a solution of the amide (assume 1.66 mmol) in 8.30 mL THF at 0 °C was added LAH (189 mg, 4.98 mmol) portionwise slowly. The reaction was heated to 70 °C and stirred for 7 h. The mixture was then cooled to 0 °C and quenched by sequential addition of 189 μl H_2O, 189 μl 15% NaOH, and 567 μl H_2O. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The product amine[88] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 1.66 mmol) in 8.30 mL CH_2Cl_2 at 23 °C was added Et_3N (463 μl, 3.32 mmol), TsCl (379 mg, 1.99 mmol), and DMAP (10.1 mg, 0.0830 mmol), sequentially. The reaction was stirred at 23 °C for 10 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford tosylamide **474** (299 mg, 67% yield over 3 steps, R_F = 0.24 in 4:1 hexanes/EtOAc) as a colorless oil. **Tosylamide 474**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74

(d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.01-4.95 (m, 1H), 4.57 (br t, *J* = 6.0 Hz, 1H), 2.92 (app.q, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 1.94 (app.q, *J* = 7.2 Hz, 2H), 1.64 (s, 3H), 1.53 (s, 3H), 1.48 (app.quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2, 133.0, 129.9, 127.3, 123.2, 43.1, 29.8, 25.9, 25.3, 21.7, 17.9; IR (film) 3283, 1325, 1160 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{22}O_2NS]^+$: 268.1371, found 268.1363.

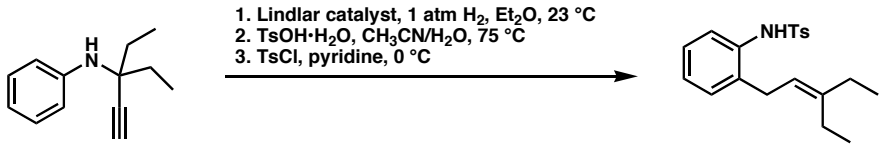


567 ***568***

Aniline 568. Aniline **568** was synthesized according to the literature procedure.[71] To a suspension of lithium acetylide ethylenediamine complex (483 mg, 4.72 mmol) in 4.72 mL THF at 35 °C was added 3-pentanone (500 μl, 4.72 mmol). The reaction mixture was stirred at 35 °C for 3 h. The mixture was then cooled to 0 °C, quenched with saturated NH_4Cl (30 mL), and extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The alcohol[89] (R_F = 0.39 in 4:1 hexanes/EtOAc) was carried crude to the next reaction.

To a solution of the propargylic alcohol (assume 4.72 mmol) in 4.72 mL CH_2Cl_2 at 23 °C was added Et_3N (711 μl, 5.10 mmol), Ac_2O (513 μl, 5.43 mmol), and DMAP (26.5 mg, 0.236 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, washed with 1 N HCl (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.59 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 4.72 mmol) in THF (6.13 mL) at 23 °C under nitrogen was added Et_3N (556 μL, 3.99 mmol), aniline (331 μL, 3.63 mmol), and CuCl (35.9 mg, 0.363 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 50 mL EtOAc and 35 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (35 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to provide aniline **568**[72] (253 mg, 37% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.



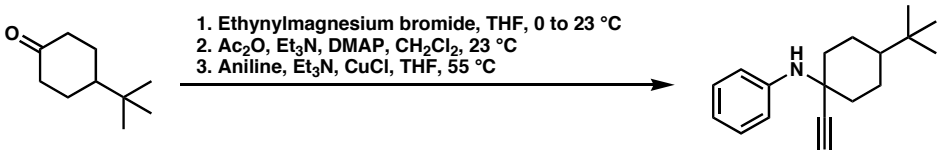
568 ***487***

Tosylaniline 487. Aniline **568** (101 mg, 0.539 mmol) was dissolved in Et_2O (2.70 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 5.4 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 20 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.68 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 0.539 mmol) in CH_3CN/H_2O (5.80 mL, 9:1) was added $TsOH•H_2O$ (10.3 mg, 0.0539 mmol). The solution was heated to 75 °C and stirred. After 8 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (50 mL),

and the organic layer was washed with brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/EtOAc eluent) afforded the rearranged aniline[72] (75.4 mg, 74% yield over 2 steps, R_F = 0.30 in 4:1 hexanes/Et_2O) as a colorless oil, which was carried on directly to the subsequent reaction.

To a solution of the free aniline (226 mg, 1.19 mmol) in 3.97 mL pyridine at 0 °C was added TsCl (273 mg, 1.43 mmol) portionwise over 1 min. The bright yellow solution was stirred at 0 °C for 1 h. The mixture was diluted with 75 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The combined aqueous layers were extracted with 40 mL EtOAc, and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (4:1 hexanes/Et_2O eluent) afforded tosylaniline **487** (329 mg, 80% yield, R_F = 0.39 in 4:1 hexanes/EtOAc) as a pale yellow oil. **Tosylaniline 487**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.19-7.15 (m, 1H), 7.11-7.05 (comp m, 2H), 6.56 (br s, 1H), 4.94 (t, *J* = 6.9 Hz, 1H), 2.99 (d, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 2.09 (q, *J* = 7.8 Hz, 2H), 2.06 (q, *J* = 7.8 Hz, 2H), 1.00 (app.t, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 143.4, 137.0, 135.3, 133.8, 130.1, 129.8, 127.5, 127.3, 126.0, 123.8, 119.2, 30.6, 29.3, 23.5, 21.8, 13.1, 12.9; IR (film) 2965, 1335, 1163 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{25}O_2NS]^+$: 343.1606, found 343.1601.



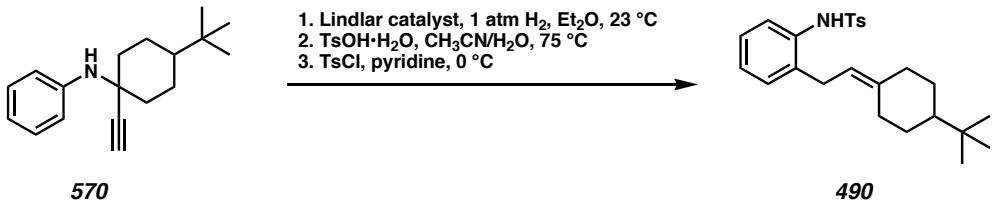
569 ***570***

Aniline 570. Ethynyl Grignard addition was performed according to the reported procedure.[90] To a solution of 4-*t*-butylcyclohexanone (500 mg, 3.24 mmol) in 16.2 mL THF at 0 °C was added ethynylmagnesium bromide (13.0 mL, 0.5 M in THF, 6.48 mmol) dropwise over 5 min. The reaction was allowed to warm to 23 °C over 15 min. After 15 min at 23 °C, the mixture was cooled to 0 °C and quenched with 1 N HCl (40 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford the *syn*-propargylic alcohol (402 mg, 69% yield, R_F = 0.13 in 9:1 hexanes/EtOAc), which was carried to the subsequent reaction. Only the major diastereomer was isolated.

To a solution of the alcohol (402 mg, 2.23 mmol) in 2.23 mL CH_2Cl_2 at 23 °C was added Et_3N (336 μl, 2.41 mmol), Ac_2O (242 μl, 2.56 mmol), and DMAP (13.7 mg, 0.112 mmol), sequentially. The reaction was stirred at 23 °C for 16 h. The reaction was then poured over saturated NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.59 in 4:1 hexanes/EtOAc) was carried on crude to the next reaction.

To a solution of the acetate (assume 2.23 mmol) in THF (2.23 mL) at 23 °C under nitrogen was added Et_3N (263 μL, 1.89 mmol), aniline (157 μL, 1.72 mmol), and CuCl (17.0 mg, 0.172 mmol), sequentially. The reaction was heated to 55 °C and stirred for 6

h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 50 mL EtOAc and 35 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (35 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide aniline **570** (403 mg, 71% yield, R_F = 0.63 and 0.70 in 4:1 hexanes/EtOAc), a mixture of diastereomers, as a white solid, which was carried on to the next reaction.



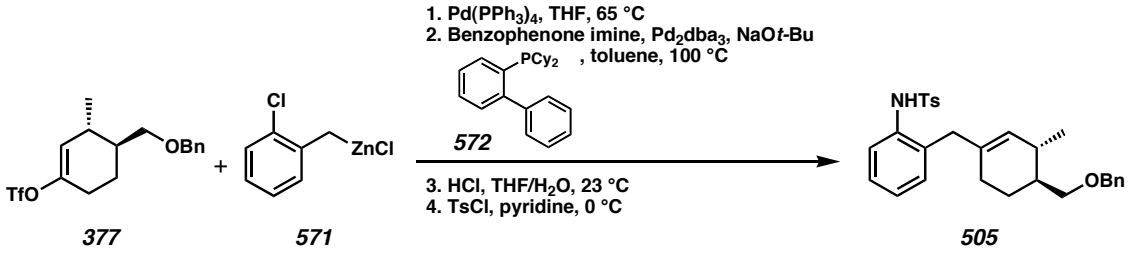
570 ***490***

Tosylaniline 490. Aniline **570** (403 mg, 1.58 mmol) was dissolved in Et_2O (7.90 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 15.8 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 1 h. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.45 and 0.80 in 4:1 hexanes/Et_2O) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 1.58 mmol) in CH_3CN/H_2O (17.2 mL, 9:1) was added $TsOH•H_2O$ (30.6 mg, 0.0161 mmol). The solution was heated to 75 °C and stirred. After 16 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (100 mL), and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and

concentrated in vacuo. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) afforded the rearranged aniline (190 mg, 47% yield over 2 steps, R_F = 0.28 in 9:1 hexanes/EtOAc) as a colorless oil, which was carried on directly to the subsequent reaction.

To a solution of the free aniline (190 mg, 0.738 mmol) in 1.48 mL pyridine at 0 °C was added TsCl (169 mg, 0.886 mmol) portionwise over 1 min. The bright yellow solution was stirred at 0 °C for 45 min. The mixture was diluted with 75 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The combined aqueous layers were extracted with 40 mL EtOAc, and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (6:1 hexanes/Et_2O eluent) afforded tosylaniline **490** (291 mg, 96% yield, R_F = 0.24 in 9:1 hexanes/EtOAc) as a pale yellow oil. **Tosylaniline 490**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.21-7.15 (m, 1H), 7.10-7.04 (comp m, 2H), 6.60 (br s, 1H), 4.91 (t, *J* = 7.2 Hz, 1H), 2.96 (d, *J* = 7.2 Hz, 2H), 2.62 (app.d, *J* = 13.2 Hz, 1H), 2.38 (s, 3H), 2.20 (app.d, *J* = 12.6 Hz, 1H), 2.06 (app.t, *J* = 10.5 Hz, 1H), 1.98-1.79 (comp m, 3H), 1.27-1.00 (comp m, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 142.8, 137.0, 135.4, 133.5, 130.2, 129.7, 127.5, 127.2, 126.0, 123.7, 117.7, 48.5, 37.1, 32.7, 30.6, 29.3, 28.7, 28.6, 27.8, 21.8; IR (film) 2945, 1164 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{25}H_{33}O_2NS]^+$: 411.2232, found 411.2228.



377 *571* *505*

Tosylaniline 505. To a solution of trifluoromethanesulfonate **377** (815 mg, 2.24 mmol) in 11.2 mL THF at 23 °C under argon was added $Pd(PPh_3)_4$ (77.7 mg, 0.0672 mmol), then 2-chlorobenzylzinc chloride (5.38 mL, 0.5 M in THF, 2.69 mmol) dropwise over 5 min. The reaction mixture was heated to 65 °C and stirred. After 90 min, the reaction was cooled to room temperature, diluted with 100 mL EtOAc, and quenched with 1 N HCl (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide the aryl chloride (767 mg, 100% yield, R_F = 0.56 in 9:1 hexanes/EtOAc) as a colorless oil.

Palladium-catalyzed aryl amination with benzophenone imine was performed according to the procedure of Wolfe et al.[91] A flame-dried sealable schlenk tube was charged with $Pd_2(dba)_3$ (49.3 mg, 0.0538 mmol), phosphine **572** (75.4 mg, 0.215 mmol), and NaO*t*-Bu (362 mg, 3.77 mmol). A solution of the aryl chloride (767 mg, 2.24 mmol) in 5.38 mL toluene was added, then benzophenone imine (542 μl, 3.23 mmol) was introduced. The reaction mixture was subjected to three freeze-pump-thaw cycles, the tube was sealed under argon, and it was heated to 100 °C. After 24 h, the reaction was cooled to room temperature, diluted with 25 mL Et_2O, and filtered through a plug of celite (1 x 5 cm, Et_2O eluent). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide the *N*-aryl

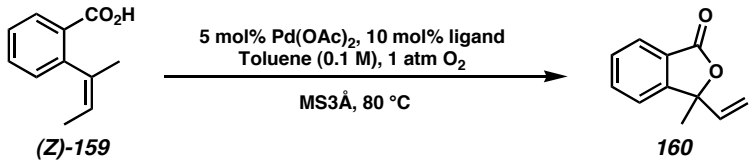
imine (R_F = 0.46 in 9:1 hexanes/EtOAc), which was immediately carried to the subsequent reaction.

To a solution of the imine (assume 2.69 mmol) in 8.97 mL THF at 23 °C was added 1.0 M HCl (897 μl, 0.897 mmol) dropwise. The reaction was stirred vigorously for 2 h, and the mixture was then partitioned between 100 mL EtOAc and 50 mL 1 N NaOH. The aqueous phase was extracted with EtOAc (50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (12:1 → 6:1 hexanes/EtOAc eluent) to provide the aniline (524 mg, 73% yield over 2 steps, R_F = 0.17 in 4:1 hexanes/Et_2O) as a colorless oil.

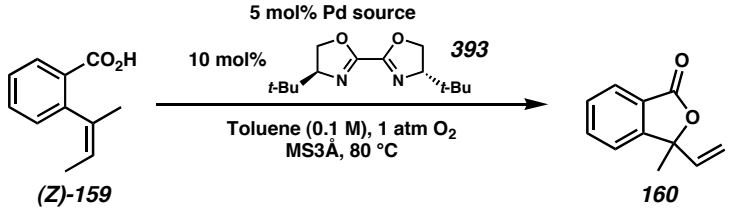
To a solution of the aniline (124 mg, 0.386 mmol) in 3.86 mL pyridine at 0 °C was added TsCl (88.3 mg, 0.463 mmol) portionwise over 1 min. The mixture was stirred for 1 h, at which point it was partitioned between 100 mL EtOAc and 40 mL 1 N HCl. The aqueous phase was extracted with EtOAc (2 x 30 mL), and the organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (8:1 hexanes/EtOAc eluent) afforded tosylaniline **505** (134 mg, 73% yield, R_F = 0.27 in 4:1 hexanes/acetone) as a colorless oil. **Tosylaniline 505**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.35-7.25 (comp m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.19 (app.t, *J* = 7.2 Hz, 1H), 7.07 (app.t, *J* = 7.5 Hz, 1H), 6.85 (br s, 1H), 5.23 (br s, 1H), 4.51 (ABq, *J* = 12.0, Δν = 16.1 Hz, 2H), 3.52 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.34 (dd, *J* = 6.9, 9.0 Hz, 1H), 2.87 (s, 2H), 2.38 (s, 3H), 2.10-2.02 (m, 1H), 1.89-1.81 (m, 1H), 1.74-1.66 (comp m, 2H), 1.52-1.32 (comp m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 138.9, 137.2, 135.9, 135.2, 131.2,

130.5, 129.8, 128.5, 127.8, 127.7, 127.7, 127.2, 125.8, 123.7, 73.3, 73.3, 41.1, 41.0, 32.5, 27.3, 25.2, 21.7, 20.7; IR (film) 1163, 1092 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{29}H_{33}NO_3S]^+$: 475.2181, found 475.2186.

5.7.3 Palladium(II) Heterocyclizations

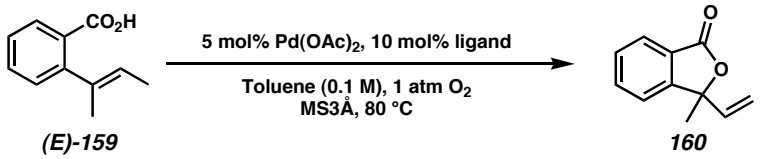


General procedure for the ligand screen in the cyclization of (*Z*)-159 (Table 5.2.1). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.3 mg, 0.00565 mmol) was added, and the solids were taken up in toluene (813 μl). Ligand (0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*Z*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method). The spectroscopic data for lactone **160** (R_F = 0.36 in 4:1 hexanes/EtOAc) was identical to that reported.[3]

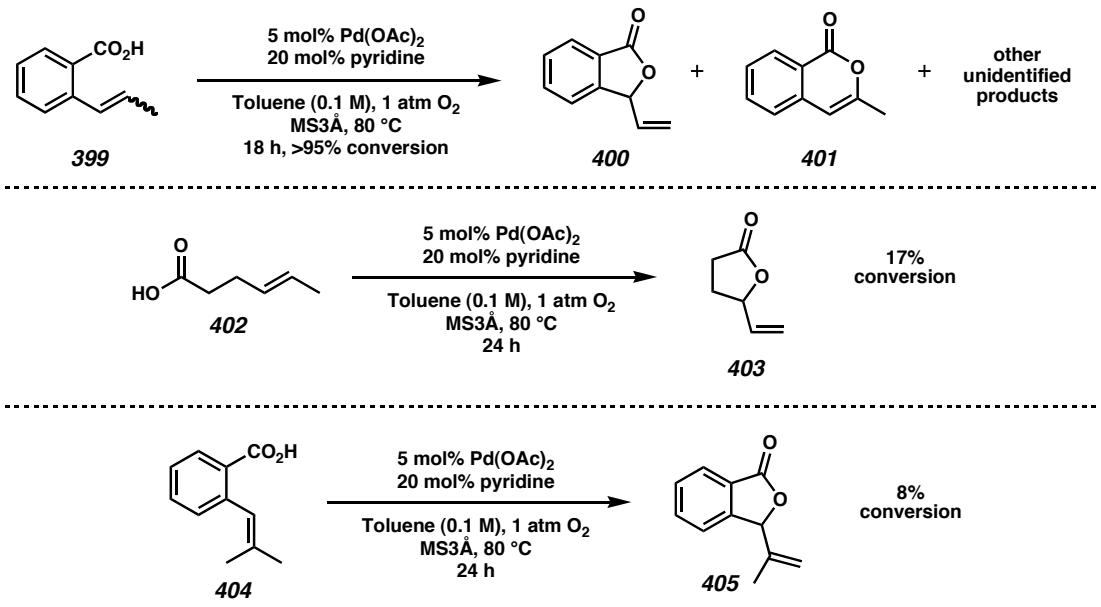


General procedure for the palladium source screen in the cyclization of (*Z*)-159 (Table 5.2.2). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, Pd source (0.00565

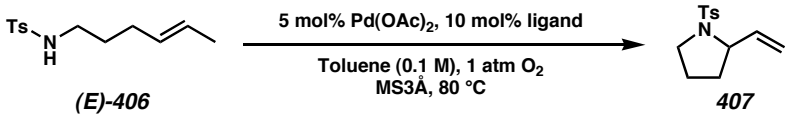
mmol) was added, and the solids were taken up in toluene (813 μl). Ligand **393** (2.9 mg, 0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*Z*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method).



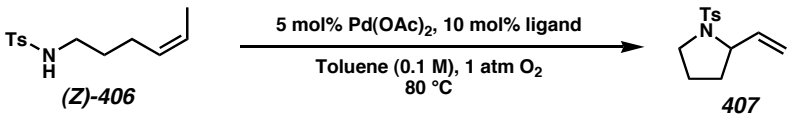
General procedure for the ligand screen in the cyclization of (*E*)-159 (Table 5.2.3). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.3 mg, 0.00565 mmol) was added, and the solids were taken up in toluene (813 μl). Ligand (0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*E*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method).



General procedure for investigation of the substrate scope of the acid cyclization (Scheme 5.2.2). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (500 mg/mmol substrate) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the solids were taken up in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of the carboxylic acid in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. Lactones **400**,[92] **401**[93] (both R_F = 0.38 in 4:1 hexanes/EtOAc), **403**[94] (R_F = 0.25 in 4:1 hexanes/Et_2O), and **405**[7c] (R_F = 0.42 in 4:1 hexanes/EtOAc) were identical spectroscopically to the literature reports.

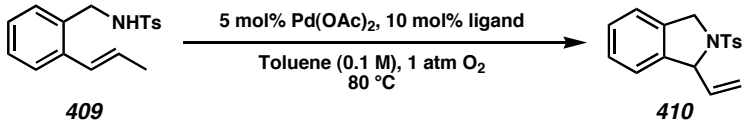


General procedure for the ligand screen in the cyclization of (*E*)-406 (Table 5.3.1). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (49.4 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00494 mmol) was added, and the solids were taken up in toluene (687 μl). Ligand (0.00987 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **(*E*)-406** (25.0 mg, 0.0987 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for pyrrolidine **407** (R_F = 0.33 in 4:1 hexanes/EtOAc) was identical to that reported.[10f]



General procedure for the ligand screen in the cyclization of (*Z*)-406 (Table 5.3.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00494 mmol) was added, and the compound was dissolved in toluene (687 μl). Ligand (0.00987 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **(*Z*)-406** (25.0 mg, 0.0987

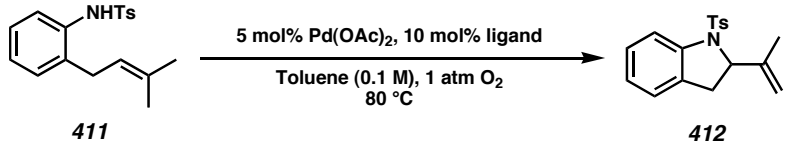
mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



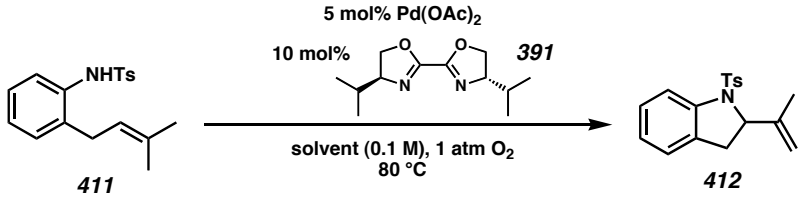
409 *410*

General procedure for the ligand screen in the cyclization of 409 (Table 5.3.3). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (695 μl). Ligand (0.00995 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **409** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). Pyrrolidine **410** (R_F = 0.38 in 4:1 hexanes/EtOAc) was further isolated by flash chromatography (5:1 hexanes/Et_2O eluent) for characterization analysis. **Pyrrolidine 410**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.25-7.23 (comp m, 2H), 7.18-7.15 (m, 1H), 7.08-7.05 (m, 1H), 5.90 (ddd, *J* = 8.1, 9.9, 17.1 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.26-5.24 (m, 1H), 5.24 (d, *J* = 9.9 Hz, 1H), 4.73 (d, *J* = 13.5 Hz, 1H), 4.63 (d, *J* = 13.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 139.0, 138.4, 135.5, 135.1, 129.9, 128.3, 128.0, 127.8, 123.6,

122.7, 116.8, 68.7, 54.0, 21.7; IR (film) 1347, 1164 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{17}NO_2S]^+$: 299.0980, found 299.0983.

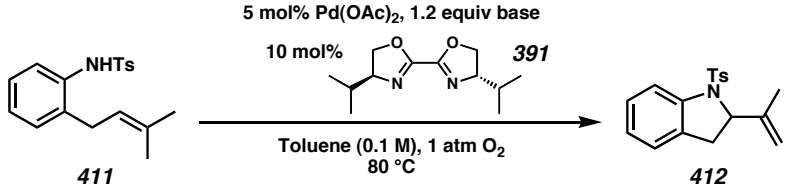


General procedure for the ligand screen in the cyclization of 411 (Table 5.3.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Ligand (0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^1H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **412** (R_F = 0.45 in 4:1 hexanes/EtOAc) was identical to that reported.[73]

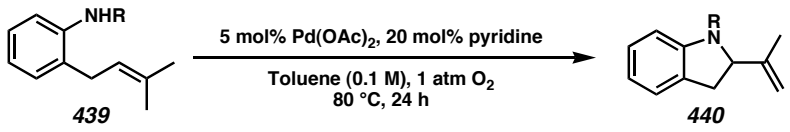


General procedure for the solvent screen in the cyclization of 411 (Table 5.3.5). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was

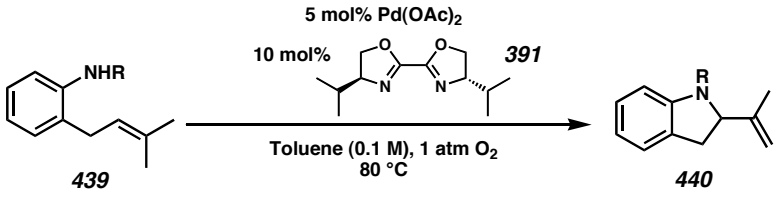
dissolved in solvent (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl solvent was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



General procedure for the base screen in the cyclization of 411 (Table 5.3.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, followed by the addition of base (0.132 mmol, 1.20 equiv), and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

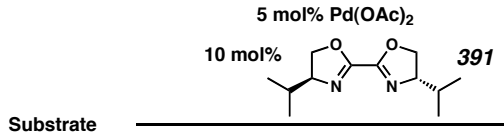


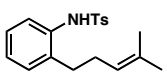
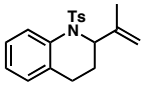
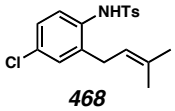
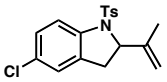
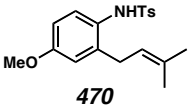
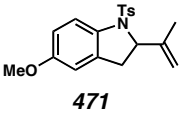
General procedure for the aniline substituent examination in the racemic cyclizations (Table 5.3.7). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The products of these reactions were verified by independent syntheses (see Section 5.7.4).



General procedure for the aniline substituent examination in the asymmetric cyclizations (Table 5.3.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Bisoxazoline **391** (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to

80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Entry	Substrate	Product	time	Conv (%)	% ee
1	 *466*	 *467*	24 h	17	11
2	 *468*	 *469*	5 h 24 h	14 19	36 33
3	 *470*	 *471*	5 h 24 h	21 30	26 18

General procedure for the asymmetric cyclizations of 466, 468, and 470 (Table 5.3.9). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Bisoxazoline **391** (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots

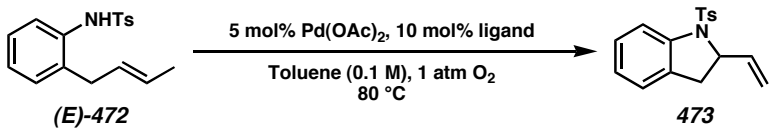
(approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

The spectroscopic data for tosylaniline **467** (R_F = 0.32 in 9:1 hexanes/EtOAc) was identical to that reported.[95]

Tosylindoline **469** (R_F = 0.43 in 4:1 hexanes/EtOAc) was further isolated by flash chromatography (6:1 hexanes/Et_2O eluent) for characterization analysis. **Tosylindoline 469**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.57 (comp m, 3H), 7.21 (d, 7.8.2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 5.06 (s, 1H), 4.87 (s, 1H), 4.66 (dd, *J* = 3.6, 10.2 Hz, 1H), 2.95 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.66 (dd, *J* = 3.6, 16.5 Hz, 1H), 2.38 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 144.1, 141.0, 135.0, 133.6, 129.9, 129.7, 128.0, 127.3, 125.3, 117.5, 112.8, 67.3, 34.3, 21.8, 17.9; IR (film) 1357, 1167 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{18}H_{18}NO_2SCl]^+$: 347.0747, found 347.0747.

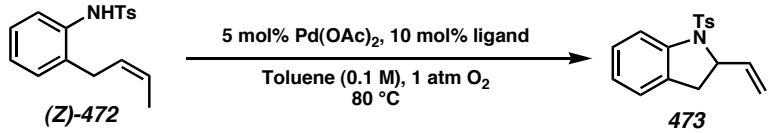
Tosylindoline **471** (R_F = 0.25 in 4:1 hexanes/acetone) was further isolated by flash chromatography (3:1 hexanes/Et_2O eluent) for characterization analysis. **Tosylindoline 471**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.75 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.58 (br s, 1H), 5.06 (br s, 1H), 4.85 (br s, 1H), 4.60 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.75 (s, 3H), 2.82 (dd, *J* = 9.9, 16.5 Hz, 1H), 2.60 (dd, *J* = 3.3, 16.5 Hz, 1H), 2.36 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 144.4, 143.9, 135.5, 135.0, 133.8, 129.7, 127.4, 118.1, 112.9, 112.3,

110.9, 67.1, 55.8, 34.5, 21.7, 18.2; IR (film) 1167 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{21}NO_3S]^+$: 343.1242, found 343.1255.



(E)-472 *473*

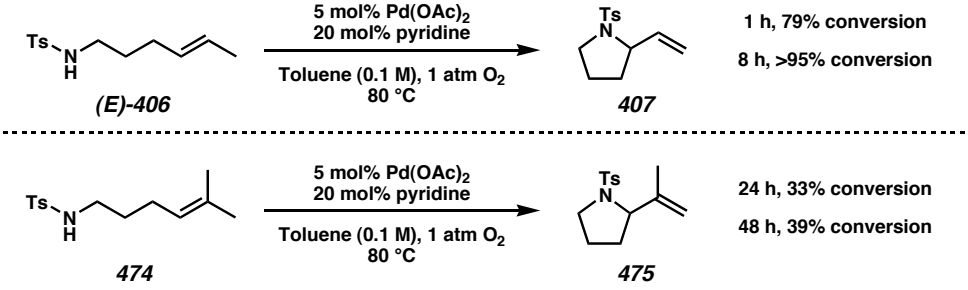
General procedure for the ligand screen in the cyclization of (*E*)-472 (Table 5.3.10). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (665 μl). Ligand (0.00995 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **(*E*)-472** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^1H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **473** (R_F = 0.31 in 2:1 hexanes/EtOAc) was identical to that reported.[11]



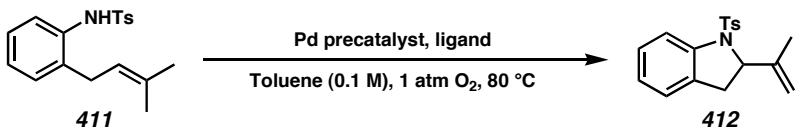
(Z)-472 *473*

General procedure for the ligand screen in the cyclization of (*Z*)-472 (Table 5.3.11). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (665 μl). Ligand (0.00995 mmol) was added, and the mixture was

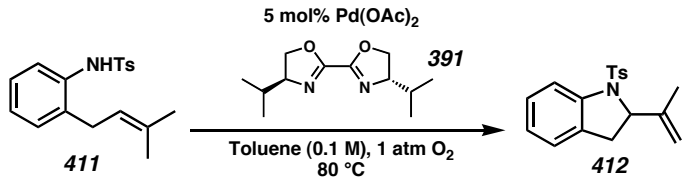
cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **(*Z*)-472** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **473** was identical to that reported.[11]



Procedure for the cyclization of (*E*)-406 and 474 (Scheme 5.3.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The spectroscopic data for pyrrolidine **475** (R_F = 0.48 in 1:1 hexanes/Et_2O) was identical to that reported.[96]

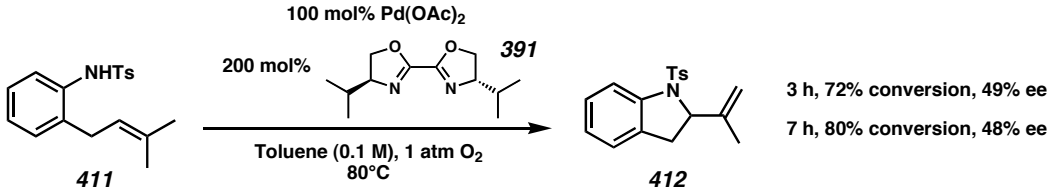


General procedure for the comparison of monodentate and bidentate ligands in the cyclization of 411 (Table 5.4.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, palladium precatalyst (0.0500–0.100 equiv) was added, and the compound was dissolved in toluene (810 μl). Ligand (0.0500 –0.200 equiv) was added if listed, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR.

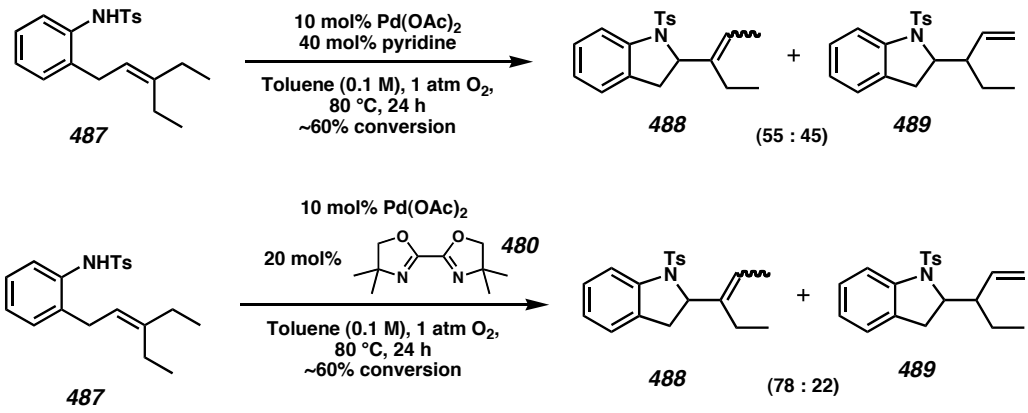


General procedure for the examination of ligand stoichiometry for the cyclization of 411 (Table 5.4.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (0.0500–1.00 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of

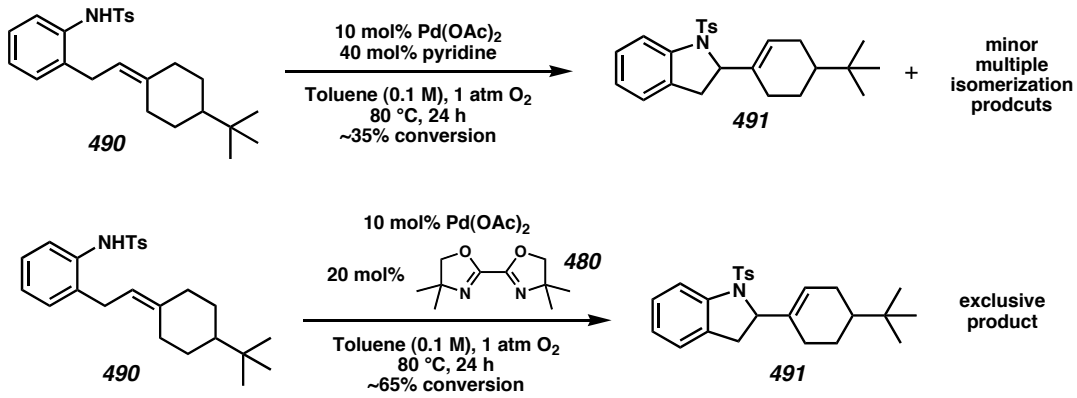
tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



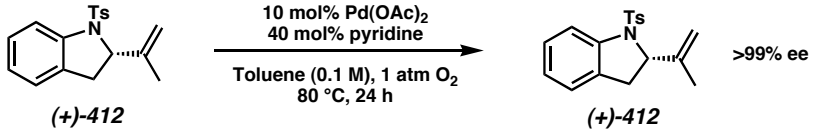
Cyclization of 411 with stoichiometric palladium (Scheme 5.4.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (7.1 mg, 0.0317 mmol) was added, and the compound was dissolved in solvent (217 μl). Bisoxazoline **391** (14.2 mg, 0.0634 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (10.0 mg, 0.0317 mmol) in 100 μl solvent was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 50 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Cyclization of 487 with either pyridine or bisoxazoline 480 as the ligand (Scheme 5.4.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.3 mg, 0.0102 mmol) was added, and the compound was dissolved in toluene (720 μl). Pyridine (3.3 μl, 0.0408 mmol) or bisoxazoline **480** (4.0 mg, 0.0204 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **487** (35.0 mg, 0.102 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The product mixture was characterized by independent syntheses of the individual compounds (see Section 5.7.4).

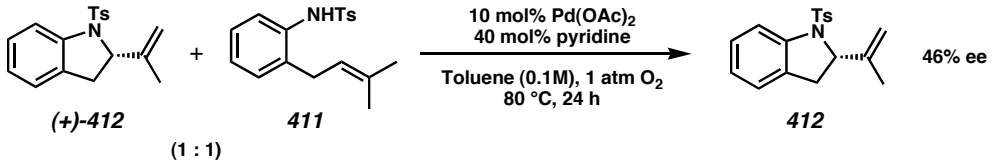


Cyclization of 490 with either pyridine or bisoxazoline 480 as the ligand (Scheme 5.4.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.2 mg, 0.00972 mmol) was added, and the compound was dissolved in toluene (672 μl). Pyridine (3.1 μl, 0.0389 mmol) or bisoxazoline **480** (3.8 mg, 0.0194 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **490** (40.0 mg, 0.0972 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The major product (**491**, R_F = 0.54 in 4:1 hexanes/EtOAc) was identical spectroscopically to the compound reported in the literature.[86]

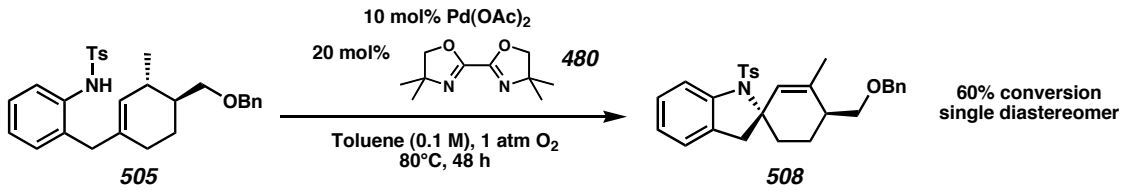


Subjection of tosylindoline (+)-412 to racemic cyclization conditions (Scheme 5.4.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.1 mg, 0.00957 mmol) was added, and the compound was

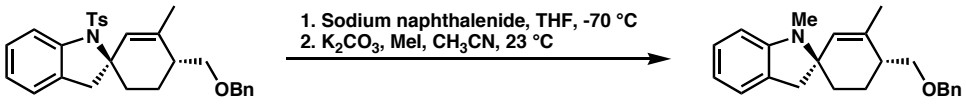
dissolved in toluene (657 μl). Pyridine (3.1 μl, 0.0383 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylindoline **(+)-412** (30.0 mg, 0.0957 mmol, see Section 5.7.4 for synthesis) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken after 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by HPLC (see Table 5.7.1 for assay method). Tosylindoline **(+)-412** was found to be >99% ee.



Racemic cyclization of 411 in the presence of (+)-412 (Scheme 5.4.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.1 mg, 0.00957 mmol) was added, and the compound was dissolved in toluene (657 μl). Pyridine (3.1 μl, 0.0383 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylindoline **(+)-412** (15.0 mg, 0.0479 mmol) and tosylaniline **411** (15.1 mg, 0.0479 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken after 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). Conversion was complete and tosylindoline **412** was measured at 46% ee.



Cyclization of 505 with bisoxazoline ligand 480 (Scheme 5.4.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.4 mg, 0.0105 mmol) was added, and the compound was dissolved in toluene (750 μl). Bisoxazoline **480** (4.1 mg, 0.0210 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **505** (50.0 mg, 0.105 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. The reaction was cooled after 48 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The crude material was purified by flash chromatography (6:1 hexanes/Et_2O eluent) to afford tosylindoline **508** (R_F = 0.44 in 2:1 hexanes/Et_2O) as a single diastereomer. **Tosylindoline 508**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.38-7.26 (comp m, 5H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.16 (app.t, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.95 (app.t, *J* = 7.5 Hz, 1H), 5.38 (s, 1H), 4.52 (app.s, 2H), 3.54 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.48 (dd, *J* = 6.0, 9.3 Hz, 1H), 3.00 (app.s, 2H), 2.55 (dt, *J* = 3.3, 12.9 Hz, 1H), 2.52-2.42 (m, 1H), 2.38 (s, 3H), 2.06-1.96 (m, 1H), 1.95-1.88 (m, 1H), 1.75-1.62 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 142.3, 139.8, 138.7, 137.4, 129.6, 129.1, 128.5, 127.8, 127.7, 127.7, 127.6, 127.1, 125.1, 123.0, 114.9, 73.3, 72.6, 72.1, 44.9, 39.2, 34.5, 24.8, 21.7, 21.5; IR (film) 1356, 1166 cm^{-1}; HRMS (EI+) *m/z* calc'd for $[C_{29}H_{31}NO_3S]^+$: 473.2025, found 473.2045.



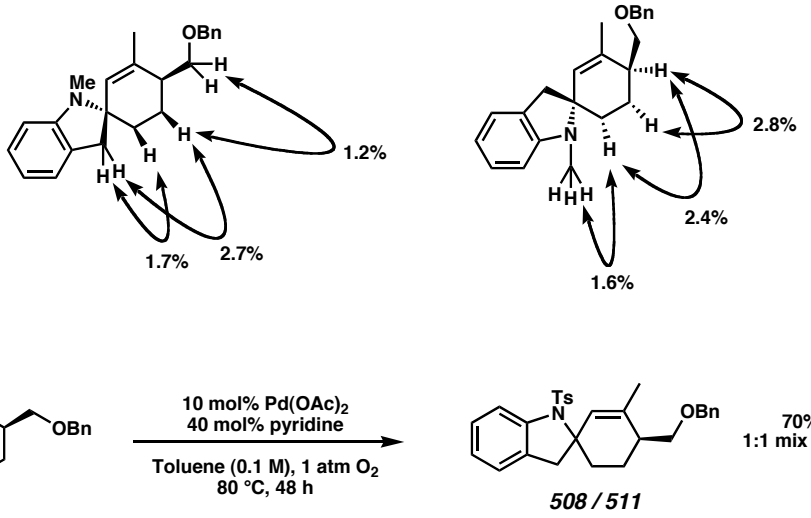
508 *573*

Derivatization of tosylindoline 508 for determination of relative stereochemistry. To a solution of tosylindoline **508** (11.8 mg, 0.0249 mmol) in 175 μl THF at –70 °C was added a solution of sodium naphthalenide (0.2 M in THF, generated from naphthalene and Na metal) dropwise until the dark green color persisted. The reaction mixture was immediately quenched with saturated NH_4Cl (15 mL), and it was allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (3:1 hexanes/Et_2O eluent) to provide the deprotected indoline (6.2 mg, 78% yield, R_F = 0.53 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the indoline (4.8 mg, 0.0150 mmol) in 543 μl CH_3CN at 23 °C was added K_2CO_3 (10.4 mg, 0.0750 mmol), then MeI (109 μl). The reaction was stirred at 23 °C for 7 h. The mixture was then diluted with 10 mL CH_2Cl_2 and filtered through a plug of celite (pipet), and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (4:1 hexanes/EtOAc eluent) to provide methyl indoline **573** (2.2 mg, 44% yield, R_F = 0.66 in 4:1 hexanes/EtOAc) as a colorless oil. **Indoline 573**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.37-7.29 (comp m, 5H), 7.01 (app.t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.57 (app.t, *J* = 7.0 Hz, 1H), 6.34 (d, *J* = 7.5 Hz, 1H), 5.45 (br s, 1H), 4.53 (ABq, *J* = 12.0, Δν = 15.2 Hz, 2H), 3.58 (dd, *J* = 3.5, 9.0 Hz, 1H), 3.52 (dd, *J* =

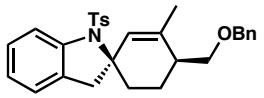
6.5, 9.5 Hz, 1H), 2.85 (ABq, J = 15.5, Δν = 9.1 Hz, 2H), 2.62 (s, 3H), 2.36-2.33 (m, 1H), 1.93-1.88 (m, 1H), 1.85-1.74 (comp m, 2H), 1.75 (s, 3H), 1.68-1.64 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 153.3, 140.0, 139.9, 130.3, 129.5, 129.4, 129.0, 128.8, 128.5, 125.0, 118.3, 107.3, 74.3, 73.3, 70.0, 44.1, 41.2, 29.9, 29.8, 25.9, 21.9; IR (film) 1607, 1486 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{23}H_{27}NO]^+$: 333.2093, found 333.2090.

Figure 5.7.1 Relevant NOE interactions for indoline **573**.



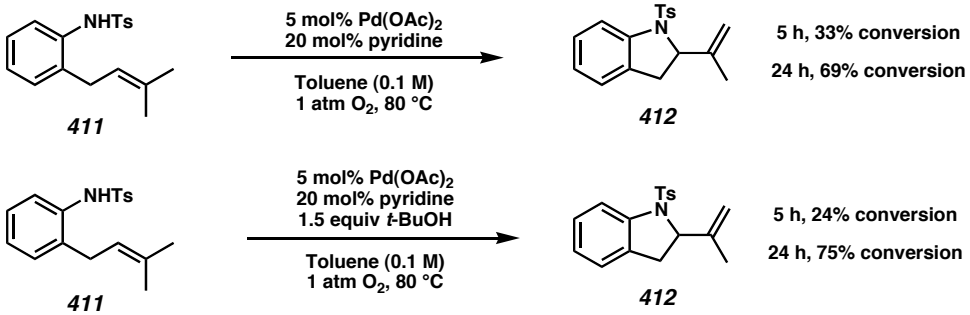
Cyclization of 505 with pyridine as the ligand (Scheme 5.4.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.4 mg, 0.0105 mmol) was added, and the compound was dissolved in toluene (750 μl). Pyridine (3.4 μl, 0.0420 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **505** (50.0 mg, 0.105 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. The reaction was cooled after 48 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The diastereomer not observed in the analogous bisoxazoline

reaction was isolated by flash chromatography (9:1 → 4:1 hexanes/Et_2O eluent) to afford tosylindoline **511** (R_F = 0.47 in 2:1 hexanes/Et_2O).



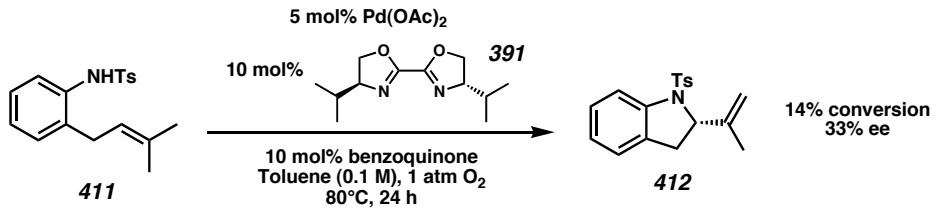
511

Tosylindoline 511: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.39-7.25 (comp m, 5H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.15 (app.t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.94 (app.t, *J* = 7.5 Hz, 1H), 5.31 (s, 1H), 4.57 (app.s, 2H), 3.70 (app.d, *J* = 7.8 Hz, 2H), 2.99 (app.s, 2H), 2.61 (dt, *J* = 2.7, 14.1 Hz, 1H), 2.38 (s, 3H), 2.36-2.28 (m, 1H), 2.10-2.02 (m, 1H), 1.78-1.65 (comp m, 2H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 142.3, 139.7, 138.8, 136.7, 129.6, 128.9, 128.6, 127.9, 127.9, 127.7, 127.4, 127.2, 125.1, 122.9, 114.6, 73.4, 72.5, 70.7, 44.7, 39.3, 30.6, 23.1, 22.9, 21.7; IR (flm) 1351, 1165, 1091 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{29}H_{32}NO_3S]^+$: 474.2103, found 474.2099.

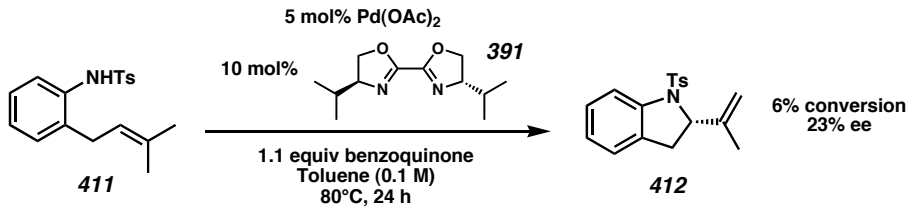


Racemic cyclization of 411 with or without added *t*-BuOH (Scheme 5.5.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Pyridine (1.8 μl, 0.0222 mmol) was added, and the mixture was cooled

to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, followed by the addition of *t*-BuOH (16.0 μl, 0.167 mmol) if necessary, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR.



Asymmetric cyclization of 411 with catalytic benzoquinone (Scheme 5.6.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, followed by the addition of benzoquinone (1.2 mg, 0.0111 mmol), and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Asymmetric cyclization of 411 with stoichiometric benzoquinone (Scheme 5.6.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, followed by the addition of benzoquinone (13.2 mg, 0.122 mmol), and the mixture was heated to 80 °C under N_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under N_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

Table 5.7.1. GC/HPLC assays for determining enantiomeric excess.

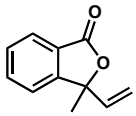
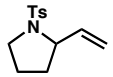
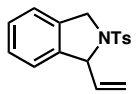
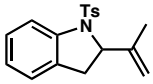
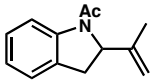
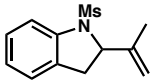
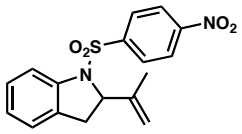
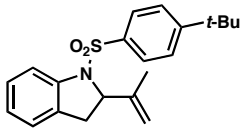
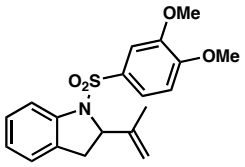
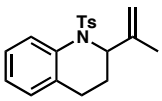
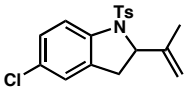
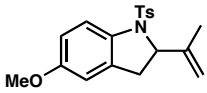
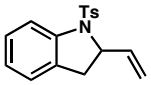
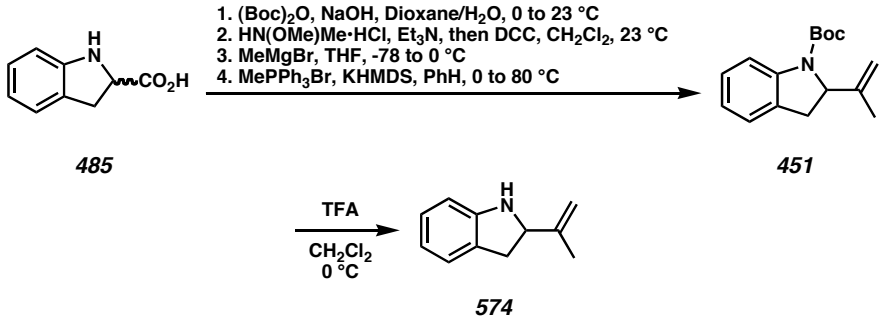
entry	Substrate	ee assay	conditions	retention times
1	 ***160***	GC Chiraldex B-DM	50 °C, 5 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	28.67, 28.85
2	 ***407***	HPLC Chiralcel AD	8% EtOH/hexane 1.0 mL/min	14.47, 18.73
3	 ***410***	HPLC Chiralcel AD	8% EtOH/hexane 1.0 mL/min	16.00, 21.62
4	 ***412***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	13.06, 23.49
5	 ***446***	HPLC Chiralcel OD-H	6% EtOH/hexane 1.0 mL/min	8.46, 12.29
6	 ***455***	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	15.97, 24.40
7	 ***459***	HPLC Chiralcel AD	4% EtOH/hexane 1.0 mL/min	17.26, 23.39
8	 ***463***	HPLC Chiralcel OD-H	3% *i*-PrOH/hexane 1.0 mL/min	7.14, 7.74

Table 5.7.1 (continued)

entry	Substrate	ee assay	conditions	retention times
9	 ***465***	HPLC Chiralcel OD-H	6% EtOH/hexane 1.0 mL/min	13.04, 14.03
10	 ***467***	HPLC Chiralcel AD	5% *i*-PrOH/hexane 1.0 mL/min	10.62, 13.79
11	 ***469***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	12.69, 21.47
12	 ***471***	HPLC Chiralcel AD	6% EtOH/hexane 1.0 mL/min	13.08, 18.84
13	 ***473***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	13.99, 20.53

5.7.4 Independent Syntheses of Heterocycles



Independent syntheses of the products from Table 5.3.7.

Carbamate 451. Carbamate synthesis was performed according to the procedure of Sato et al.[97] To a suspension of indoline-2-carboxylic acid (200 mg, 1.23 mmol) in 1.23 mL dioxane and 2.46 mL 0.5 M NaOH at 0 °C was added a solution of di-*tert*-butyl dicarbonate (295 mg, 1.35 mmol) in 1.35 mL dioxane. The reaction mixture was allowed to warm to 23 °C and stirred for 16 h. The mixture was then partitioned between 30 mL hexanes and 50 mL 0.5 M NaOH. The aqueous phase was acidified with saturated citric acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) to provide the carbamate (301 mg, 93% yield, R_F = 0.27 in 9:1 CH_2Cl_2/MeOH) as a brown oil.

To a solution of the carbamate (301 mg, 1.14 mmol) in 6.16 mL CH_2Cl_2 was added *N*,*O*-dimethylhydroxylamine hydrochloride (111 mg, 1.14 mmol), then Et_3N (159 μl, 1.14 mmol). After stirring for 5 min, DCC (235 mg, 1.14 mmol) was added. A white solid began to precipitate. After 2.5 h, the solvent was removed via rotary evaporation, and the solid residue was triturated with acetone (4 x 20 mL). The solution was then concentrated in vacuo. The crude material was purified by flash chromatography (2:1

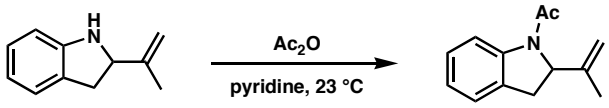
hexanes/EtOAc) to provide the Weinreb amide (276 mg, 79% yield, R_F = 0.68 in 3:1 EtOAc/hexanes), which was carried on to the subsequent reaction.

Grignard reagent addition to the Weinreb amide was performed according to the procedure of Toda et al.[98] To a solution of the amide (1.21 g, 3.95 mmol) in 39.5 mL THF was added MeMgBr (3.97 mL, 3.0 M in Et_2O, 11.9 mmol) dropwise over 5 min. The reaction was warmed to 0 °C and stirred for 3 h. The mixture was then quenched with saturated NH_4Cl (75 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (75 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide the methyl ketone (920 mg, 89% yield, R_F = 0.60 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

To a suspension of $MePPh_3Br$ (3.79 g, 10.6 mmol) in 19.5 mL PhH at 23 °C was added KHMDS (2.11 g, 10.6 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the methyl ketone (920 mg, 3.52 mmol) in 9.78 mL PhH was added dropwise over 5 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 150 mL Et_2O and 50 mL H_2O. The organic layer was washed with H_2O (2 x 50 mL) and then brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/Et_2O eluent) provided the olefin (866 mg, 95% yield, R_F = 0.58 in 4:1 hexanes/EtOAc) as a white solid. **Carbamate 451**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.17 (app.t, *J* = 7.5 Hz, 1H), 7.11 (d, 1H), 6.93 (app.t, *J* = 7.2 Hz, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 4.81-4.75 (m, 1H), 3.42 (dd, *J* = 10.5, 16.2 Hz, 1H), 2.79 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.67 (s,

3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 145.6, 130.1, 127.7, 124.8, 122.7, 122.5, 115.0, 109.9, 80.9, 64.1, 34.6, 28.6, 18.1; IR (film) 1703, 1485, 1388 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}NO_2]^+$: 259.1572, found 259.1576.

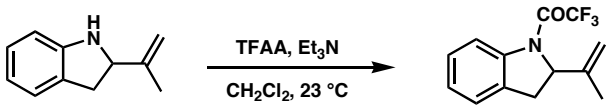
Indoline 574. To a solution of the olefin (137 mg, 0.528 mmol) in 1.32 mL CH_2Cl_2 at 0 °C was added 1.32 mL TFA dropwise. The reaction was maintained at 0 °C for 30 min, at which point it was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. The free indoline[99] (**574**, R_F = 0.47 in 4:1 hexanes/Et_2O) was sufficiently pure to use in further reactions.



574 *446*

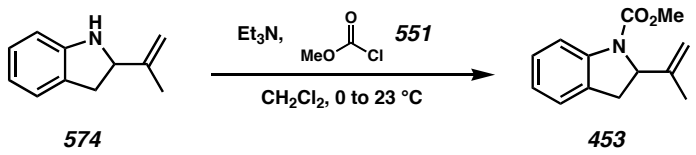
Acetanilide 446. To a solution of indoline **574** (14.9 mg, 0.0936 mmol) in 312 μl pyridine at 23 °C was added Ac_2O (17.6 μl, 0.187 mmol). The mixture was stirred at 23 °C for 30 min, at which point it was diluted with 30 mL EtOAc and washed with 0.5 N HCl (25 mL). The aqueous phase was extracted with EtOAc (30 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford the acetanilide (R_F = 0.49 in 1:1 hexanes/EtOAc) as a colorless oil. **Acetanilide 446**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.20 (app.t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.01 (app.t, *J* = 7.2 Hz, 1H), 4.85 (br s, 2H), 4.74 (br d, *J* = 9.9 Hz, 1H), 3.53 (br dd, *J* = 10.5, 16.5 Hz, 1H), 2.87 (br d, *J* = 15.9 Hz, 1H), 2.18 (br s, 3H), 1.69 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 144.6, 143.3, 130.0, 127.8,

124.6, 124.0, 117.3, 111.6, 65.1, 35.3, 23.9, 18.1; IR (film) 1662, 1482, 1396 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{15}NO]^+$: 201.1154, found 201.1149.

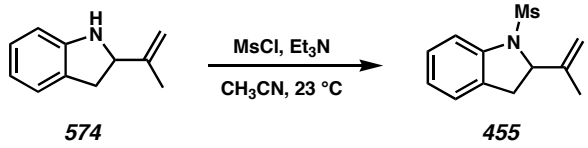


574 ***448***

Trifluoroacetanilide 448. To a solution of indoline **574** (22.0 mg, 0.138 mmol) and Et_3N (67.3 μl, 0.483 mmol) in 690 μl CH_2Cl_2 at 23 °C was added trifluoroacetic anhydride (68.2 μl, 0.483 mmol) dropwise. The solution was maintained at 23 °C for 30 min, and then it was quenched with 30 mL H_2O and extracted with CH_2Cl_2 (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to provide trifluoroacetanilide **448** (R_F = 0.40 in 1:1 hexanes/CH_2Cl_2) as a white solid. **Trifluoroacetanilide 448**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 1H), 7.29 (app.t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16 (app.t, *J* = 7.5 Hz, 1H), 5.05 (br d, *J* = 9 Hz, 1H), 4.78 (s, 1H), 4.71 (s, 1H), 3.56 (dd, *J* = 9.3, 15.6 Hz, 1H), 2.93 (d, *J* = 15.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 142.2, 130.7, 128.1, 126.2, 125.3, 118.2, 118.2, 114.3, 110.9, 64.2, 35.9, 19.0; IR (film) 1691, 1202 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{12}NOF_3]^+$: 255.0871, found 255.0881.

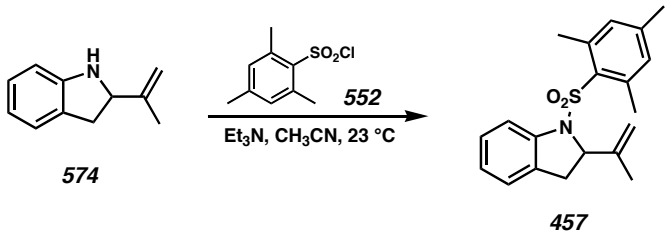


Carbamate 453. To a solution of indoline **574** (17.3 mg, 0.109 mmol) in 653 μl CH_2Cl_2 at 0 °C was added Et_3N (18.3 μl, 0.131 mmol), then methyl chloroformate (10.1 μl, 0.131 mmol). The reaction was allowed to warm to 23 °C and stirred for 16 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to afford the methyl carbamate (R_F = 0.33 in 4:1 hexanes/Et_2O) as a colorless oil. **Carbamate 453**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.19 (app.t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.96 (app.t, *J* = 7.5 Hz, 1H), 4.85 (m, 1H), 4.81 (br s, 1H), 4.76 (br s, 1H), 3.81 (s, 3H), 3.45 (dd, *J* = 10.5, 16.2 Hz, 1H), 2.82 (dd, *J* = 3.0, 16.2 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 144.9, 127.8, 124.9, 123.0, 115.1, 110.2, 64.0, 52.8, 34.7, 18.1; IR (film) 1710, 1486, 1387 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{15}NO_2]^+$: 217.1103, found 217.1105.



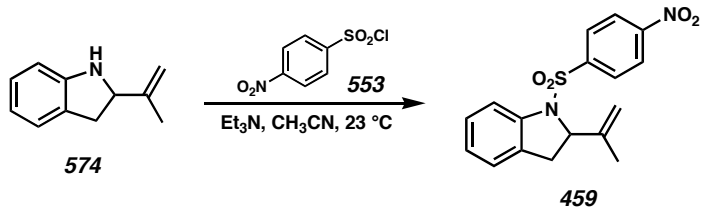
Sulfonamide 455. To a solution of indoline **574** (20.4 mg, 0.128 mmol) in 985 μl CH_3CN at 23 °C was added Et_3N (21.5 μl, 0.154 mmol), then methanesulfonyl chloride (11.9 μl, 0.154 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The

combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide indoline **455** (R_F = 0.10 in 9:1 hexanes/EtOAc) as a pale yellow oil. **Sulfonamide 455**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 1H), 7.23-7.17 (comp m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 5.07 (s, 1H), 4.88 (s, 1H), 4.82 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.50 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.90 (dd, *J* = 3.9, 16.5 Hz, 1H), 2.89 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 142.1, 130.6, 128.3, 125.4, 124.2, 114.8, 112.9, 67.2, 37.1, 34.9, 17.6; IR (film) 1347, 1158 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{15}NO_2S]^+$: 237.0823, found 237.0820.



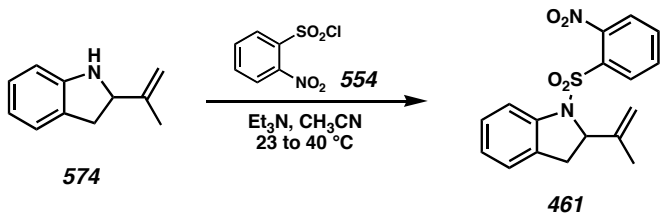
Sulfonamide 457. To a solution of indoline **574** (13.9 mg, 0.0873 mmol) in 672 μl CH_3CN at 23 °C was added Et_3N (14.6 μl, 0.105 mmol), then 2-mesitylenesulfonyl chloride (24.4 mg, 0.105 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide indoline **457** (R_F = 0.36 in 4:1 hexanes/Et_2O) as a white solid. **Sulfonamide 457**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.13-7.07 (comp m, 2H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.93 (s, 2H), 4.84 (s, 1H), 4.78 (dd, *J* = 3.0, 10.2 Hz, 1H), 4.67 (s, 1H), 3.44 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.77 (dd, *J* = 3.0, 16.2 Hz, 1H), 2.60 (s, 6H), 2.29 (s, 3H),

1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 143.1, 140.7, 133.4, 132.3, 130.1, 127.7, 125.1, 123.6, 115.3, 112.4, 66.5, 35.1, 23.1, 21.2, 17.4; IR (film) 1158 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1454.

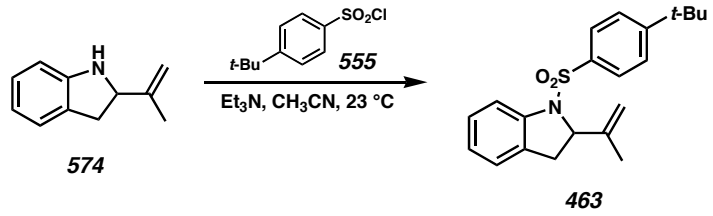


574 459

Sulfonamide 459. To a solution of indoline **574** (13.6 mg, 0.0854 mmol) in 657 μl CH_3CN at 23 °C was added Et_3N (14.2 μl, 0.102 mmol), then 4-nitrobenzenesulfonyl chloride (22.6 mg, 0.102 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to provide indoline **459** (R_F = 0.32 in 2:1 hexanes/Et_2O) as a yellow solid. **Sulfonamide 459**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.27-7.22 (m, 1H), 7.09-7.04 (comp m, 2H), 5.08 (s, 1H), 4.89 (s, 1H), 4.71 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.03 (dd, *J* = 9.9, 16.5 Hz, 1H), 2.74 (dd, *J* = 3.3, 16.5 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 143.9, 143.8, 141.2, 131.4, 128.5, 128.3, 125.5, 125.3, 124.4, 116.2, 113.1, 67.3, 34.4, 17.8; IR (film) 1530, 1350, 1172 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{16}N_2O_4S]^+$: 344.0831, found 344.0822.

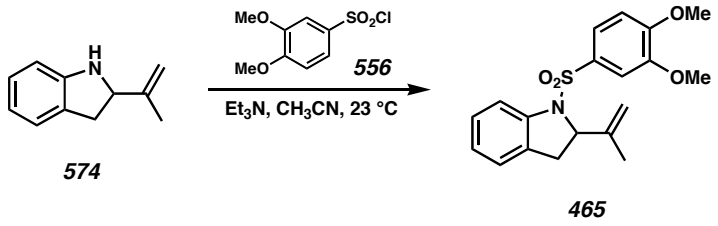


Sulfonamide 461. To a solution of indoline **574** (14.5 mg, 0.0911 mmol) in 701 μl CH_3CN at 23 °C was added Et_3N (15.2 μl, 0.109 mmol), then 2-nitrobenzenesulfonyl chloride (24.2 mg, 0.109 mmol). The reaction was heated to 40 °C and stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide indoline **461** (R_F = 0.08 in 2:1 hexanes/Et_2O) as an orange solid. **Sulfonamide 461**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.69-7.53 (comp m, 3H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.19 (app.t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.03 (app.t, *J* = 7.5 Hz, 1H), 5.07 (br s, 1H), 5.05 (dd, *J* = 2.1, 10.2 Hz, 1H), 4.83 (br s, 1H), 3.40 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.80 (dd, *J* = 2.1, 16.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 144.2, 140.8, 134.1, 131.9, 131.5, 131.5, 131.5, 128.0, 125.5, 124.8, 124.4, 115.3, 112.5, 67.4, 34.5, 18.1; IR (film) 1544, 1371, 1170 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{16}N_2O_4S]^+$: 344.0831, found 344.0840.

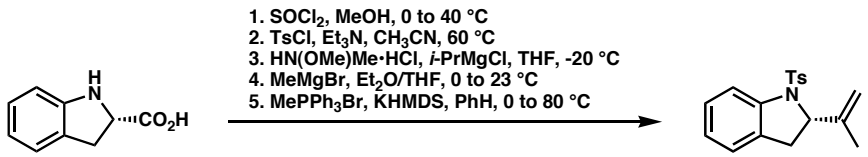


574 463

Sulfonamide 463. To a solution of indoline **574** (14.0 mg, 0.0879 mmol) in 676 μl CH_3CN at 23 °C was added Et_3N (14.6 μl, 0.105 mmol), then 4-*tert*-butylbenzenesulfonyl chloride (24.4 mg, 0.105 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide indoline **463** (R_F = 0.36 in 4:1 hexanes/Et_2O) as a white solid. **Sulfonamide 463**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.21 (app.t, *J* = 7.5 Hz, 1H), 7.06-6.98 (comp m, 2H), 5.07 (s, 1H), 4.86 (s, 1H), 4.66 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.02 (dd, *J* = 10.2, 16.2 Hz, 1H), 2.71 (dd, *J* = 4.2, 16.2 Hz, 1H), 1.70 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 144.6, 142.3, 135.3, 131.5, 128.0, 127.2, 126.1, 125.0, 124.4, 116.4, 112.5, 67.0, 35.3, 34.6, 31.2, 17.8; IR (film) 1356, 1171 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{25}NO_2S]^+$: 355.1606, found 355.1610.



Sulfonamide 465. To a solution of indoline **574** (17.9 mg, 0.112 mmol) in 862 μl CH_3CN at 23 °C was added Et_3N (18.7 μl, 0.134 mmol), then 3,4-dimethoxybenzenesulfonyl chloride (31.7 mg, 0.134 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (2:1 CH_2Cl_2/hexanes eluent) to provide indoline **465** (R_F = 0.13 in 2:1 hexanes/Et_2O) as a colorless oil. **Sulfonamide 465**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.21 (app.t, *J* = 6.0 Hz, 1H), 7.03 (app.t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.98 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 4.60 (dd, *J* = 3.6, 9.9 Hz, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 2.91 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.67 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 148.9, 144.5, 142.4, 132.1, 129.7, 127.8, 125.1, 124.8, 121.2, 117.1, 112.4, 110.5, 109.6, 66.9, 56.3, 56.1, 34.4, 18.0; IR (film) 1509, 1264, 1162 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{21}NO_4S]^+$: 359.1191, found 359.1188.



(–)-485 *(+)-412*

Independent synthesis of enantiopure (+)-412. Methyl (*S*)-indoline-2-carboxylate was synthesized according to the procedure of Jones et al.[100] To a solution of (*S*)-indoline-2-carboxylic acid (500 mg, 3.06 mmol) in 2.55 mL MeOH at 0 °C was added $SOCl_2$ (268 μl, 3.67 mmol) dropwise over 3 min. The reaction was heated to 40 °C and stirred. After 4 h, the mixture was cooled to 0 °C and quenched with H_2O (30 mL). Saturated $NaHCO_3$ was added to basify the mixture, and it was extracted with EtOAc (100 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the methyl ester (519 mg, 96% yield, R_F = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the methyl ester (519 mg, 2.93 mmol) in 22.5 mL CH_3CN at 23 °C was added Et_3N (449 μl, 3.22 mmol), then TsCl (614 mg, 3.22 mmol). The mixture was heated to 60 °C and stirred for 5 h. The red mixture was then cooled to room temperature and quenched with saturated NH_4Cl/H_2O (1:1, 30 mL), and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided the tosylindoline[101] (759 mg, 78% yield, R_F = 0.19 in 4:1 hexanes/EtOAc) as a colorless oil.

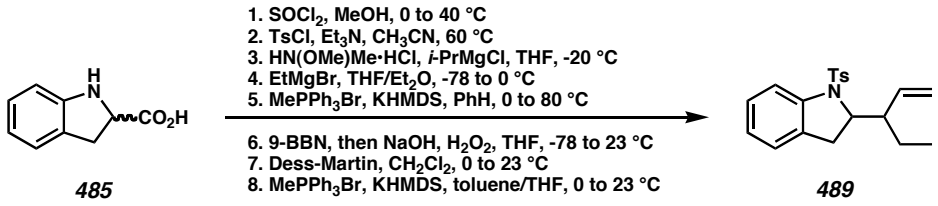
The Weinreb amide synthesis was performed according to the procedure of Williams et al.[102] To a solution of the tosylindoline (348 mg, 1.05 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (153 mg, 1.57 mmol) in 2.10 mL THF at –20 °C

was added *i*-PrMgCl (1.58 mL, 2.0 M in THF, 3.16 mmol) dropwise over 2 min. The mixture was stirred for 30 min at –20 °C, quenched with 30 mL saturated NH_4Cl, and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford the Weinreb amide (255 mg, 67% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of MeMgBr (461 μl, 3.0 M in Et_2O, 1.38 mmol) in 3.07 mL THF at –78 °C was added a solution of the Weinreb amide (166 mg, 0.461 mmol) in 1.54 mL THF dropwise over 2 min. The reaction was allowed to warm to 0 °C. After 30 min at 0 °C, the mixture was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 50 mL). The organic phases were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the methyl ketone (145 mg, 99% yield, R_F = 0.32 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a suspension of $MePPh_3Br$ (493 mg, 1.38 mmol) in 2.56 mL PhH at 23 °C was added KHMDS (275 mg, 1.38 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the methyl ketone (145 mg, 0.461 mmol) in 1.28 mL PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 75 mL Et_2O and 40 mL H_2O. The organic layer was washed with H_2O (2 x 30 mL) and then brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent)

provided the olefin[73] (142 mg, 98% yield, R_F = 0.41 in 4:1 hexanes/EtOAc) as a white semisolid. **Optical rotation of (+)-412**: $[\alpha]^{23}_D$ +141.36° (*c* 1.0, $CHCl_3$).



485 ***489***

Independent synthesis of the products from Scheme 5.4.4.

Tosylindoline 489. Methyl indoline-2-carboxylate was synthesized according to the procedure of Jones et al.[100] To a solution of indoline-2-carboxylic acid (500 mg, 3.06 mmol) in 2.55 mL MeOH at 0 °C was added $SOCl_2$ (268 μl, 3.67 mmol) dropwise over 3 min. The reaction was heated to 40 °C and stirred. After 4 h, the mixture was cooled to 0 °C and quenched with H_2O (30 mL). Saturated $NaHCO_3$ was added to basify the mixture, and it was extracted with EtOAc (100 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the methyl ester (536 mg, 99% yield, R_F = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the methyl ester (536 mg, 3.02 mmol) in 23.2 mL CH_3CN at 23 °C was added Et_3N (463 μl, 3.32 mmol), then TsCl (633 mg, 3.32 mmol). The mixture was heated to 60 °C and stirred for 5 h. The red mixture was then cooled to room temperature, quenched with saturated NH_4Cl/H_2O (1:1, 30 mL), and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in

vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided the tosylindoline[101] (837 mg, 84% yield, R_F = 0.19 in 4:1 hexanes/EtOAc) as a colorless oil.

The Weinreb amide synthesis was performed according to the procedure of Williams et al.[102] To a solution of the tosylindoline (837 mg, 2.53 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (371 mg, 3.80 mmol) in 5.06 mL THF at –20 °C was added *i*-PrMgCl (3.80 mL, 2.0 M in THF, 7.59 mmol) dropwise over 2 min. The mixture was stirred for 30 min at –20 °C, quenched with 60 mL saturated NH_4Cl, and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford the Weinreb amide (821 mg, 90% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of the Weinreb amide (365 mg, 1.01 mmol) in 10.1 mL THF at –78 °C was added EtMgBr (1.01 mL, 3.0 M in Et_2O, 3.03 mmol) dropwise over 2 min. The reaction was allowed to warm to 0 °C. After 45 min at 0 °C, the mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 x 75 mL). The organic phases were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the ethyl ketone (329 mg, 99% yield, R_F = 0.53 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

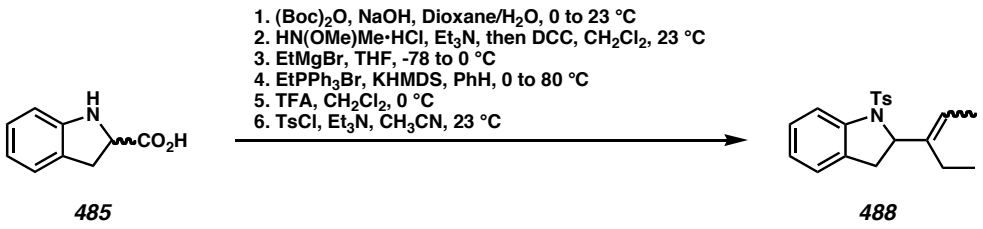
To a suspension of $MePPh_3Br$ (249 mg, 0.696 mmol) in 1.29 mL PhH at 23 °C was added KHMDS (139 mg, 0.696 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the ethyl ketone (76.4 mg, 0.232 mmol) in 643 μl PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30

min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (2 x 20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/CH_2Cl_2 → 9:9:2 hexanes/CH_2Cl_2/EtOAc eluent) provided the olefin (35.8 mg, 47% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of the olefin (35.8 mg, 0.109 mmol) in 559 μl THF at –78 °C was added 9-BBN (828 μl, 0.5 M in THF, 0.414 mmol) dropwise over 2 min. The mixture was stirred for 10 min, then allowed to warm to 23 °C. After 2.5 h, the reaction was cooled to 0 °C and quenched by addition of 373 μl EtOH, 187 μl 3 M NaOH, and 187 μl H_2O_2 (30% aq.), sequentially. The mixture was stirred at room temperature for 7 h, then diluted with EtOAc (50 mL) and washed with 1 N NaOH (2 x 25 mL), then saturated NH_4Cl (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) afforded the primary alcohol (26.6 mg, 71% yield, R_F = 0.31 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (26.6 mg, 0.0770 mmol) in 2.57 mL CH_2Cl_2 at 0 °C was added Dess-Martin periodinane (91.6 mg, 0.216 mmol). The reaction was stirred for 20 min, then allowed to warm to 23 °C. After 5 h, the mixture was diluted with 30 mL EtOAc and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (7:1 hexanes/EtOAc) to afford the aldehyde (13.9 mg, 53% yield, R_F = 0.61 in 2:1 hexanes/EtOAc), which was carried to the next reaction.

To a suspension of $MePPh_3Br$ (21.7 mg, 0.0608 mmol) in 529 μl toluene at 23 °C was added KHMDS (12.1 mg, 0.0608 mmol). The yellow mixture was stirred for 30 min, then cooled to 0 °C. A solution of the aldehyde (13.9 mg, 0.0405 mmol) in 203 μl THF was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C. After 20 min at 23 °C, the mixture was partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/Et_2O eluent) provided the olefin (7.9 mg, 57% yield, R_F = 0.53 in 4:1 hexanes/EtOAc) as a white solid. **Tosylindoline 489** (characterized as a 57:43 mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.23-7.16 (comp m, 2H), 7.12 (d, *J* = 7.8 Hz, 4H), 7.05-6.95 (comp m, 4H), 5.56-5.41 (comp m, 2H), 5.07-4.98 (comp m, 4H), 4.25 (app.quintet, *J* = 4.2 Hz, 1H), 4.13 (ddd, *J* = 2.1, 7.5, 9.0 Hz, 1H), 2.67-2.41 (comp m, 4H), 2.34 (s, 6H), 2.30-2.12 (comp m, 2H), 1.87-1.74 (m, 1H), 1.68-1.54 (m, 1H), 1.46-1.21 (comp m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 142.1, 137.7, 137.7, 135.5, 135.3, 133.6, 133.6, 129.9, 129.6, 127.7, 127.3, 127.3, 125.2, 125.2, 124.9, 124.8, 118.7, 118.4, 118.0, 117.4, 65.7, 52.3, 50.9, 31.8, 31.5, 23.7, 21.8, 21.7, 12.1, 12.0; IR (film) 1353, 1168 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1447.



485 ***488***

Tosylindoline 488. Carbamate synthesis was performed according to the procedure of Sato et al.[97] To a suspension of indoline-2-carboxylic acid (200 mg, 1.23 mmol) in 1.23 mL dioxane and 2.46 mL 0.5 M NaOH at 0 °C was added a solution of di-*tert*-butyl dicarbonate (295 mg, 1.35 mmol) in 1.35 mL dioxane. The reaction mixture was allowed to warm to 23 °C and stirred for 16 h. The mixture was then partitioned between 30 mL hexanes and 50 mL 0.5 M NaOH. The aqueous phase was acidified with saturated citric acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) to provide the carbamate (301 mg, 93% yield, R_F = 0.27 in 9:1 CH_2Cl_2/MeOH) as a brown oil.

To a solution of the carbamate (301 mg, 1.14 mmol) in 6.16 mL CH_2Cl_2 was added *N*,*O*-dimethylhydroxylamine hydrochloride (111 mg, 1.14 mmol), then Et_3N (159 μl, 1.14 mmol). After stirring for 5 min, DCC (235 mg, 1.14 mmol) was added. A white solid began to precipitate. After 2.5 h, the solvent was removed via rotary evaporation, and the solid residue was triturated with acetone (4 x 20 mL). The solution was then concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc) to provide the Weinreb amide (276 mg, 79% yield, R_F = 0.68 in 3:1 EtOAc/hexanes), which was carried on to the subsequent reaction.

Grignard reagent addition to the Weinreb amide was performed according to the procedure of Toda et al.[98] To a solution of the amide (425 mg, 1.39 mmol) in 13.9 mL

THF was added EtMgBr (1.39 mL, 3.0 M in Et_2O, 4.17 mmol) dropwise over 2 min. The reaction was warmed to 0 °C and stirred for 3.5 h. The mixture was then quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 75 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent) to provide the ethyl ketone (186 mg, 49% yield, R_F = 0.68 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

To a suspension of $EtPPh_3Br$ (133 mg, 0.357 mmol) in 662 μl PhH at 23 °C was added KHMDS (71.2 mg, 0.357 mmol). The mixture was stirred for 15 min, then cooled to 0 °C. A solution of the ethyl ketone (32.9 mg, 0.119 mmol) in 331 μl PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (2 x 20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/CH_2Cl_2 → 2:1 hexanes/CH_2Cl_2 w/ 5% EtOAc eluent) provided the mixture of cis and trans olefins (25.3 mg, 74% yield, R_F = 0.44 in 9:1 hexanes/EtOAc) as a white solid.

To a solution of the olefin (25.3 mg, 0.0880 mmol) in 440 μl CH_2Cl_2 at 0 °C was added 440 μl TFA dropwise. The reaction was maintained at 0 °C for 30 min, at which point it was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. The free indoline (R_F = 0.51 in 9:1 hexanes/EtOAc) was carried to the next reaction without further purification.

To a solution of the indoline (assume 0.0880 mmol) in 677 μl CH_3CN at 23 °C was added Et_3N (14.8 μl, 0.106 mmol), then TsCl (20.2 mg, 0.106 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide tosylindoline **488** (17.9 mg, 60% yield over 2 steps, R_F = 0.27 in 9:1 hexanes/EtOAc) as a white solid. **Tosylindoline 488** (characterized as a 58:42 mixture of olefin isomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.55 (comp m, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.32-7.15 (comp m, 6H), 7.04-6.95 (comp m, 4H), 5.52 (q, *J* = 6.9 Hz, 1H), 5.31 (q, *J* = 6.9 Hz, 1H), 5.18 (dd, *J* = 4.8, 10.8 Hz, 1H), 4.67 (dd, *J* = 3.3, 10.2 Hz, 1H), 3.13 (dd, *J* = 10.5, 16.5 Hz, 1H), 2.95 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.64 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.62 (dd, *J* = 5.1, 16.5 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.09-1.92 (comp m, 4H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 7.8 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 143.8, 142.8, 142.4, 142.0, 141.0, 135.6, 135.2, 132.1, 131.6, 129.9, 129.8, 129.7, 128.7, 127.9, 127.8, 127.4, 127.3, 125.1, 124.9, 124.5, 124.1, 122.6, 120.9, 118.7, 116.8, 116.0, 67.0, 60.9, 35.2, 35.1, 23.1, 21.7, 20.6, 13.6, 13.3, 13.2, 12.3; IR (film) 1356, 1169 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1436.

5.8 Notes and References

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(9) We also investigated other standard reaction parameters. Lowering the temperature slowed the reaction rate, but did not increase enantioselectivity. Toluene appeared to be the optimal solvent for these reactions among the solvents screened.

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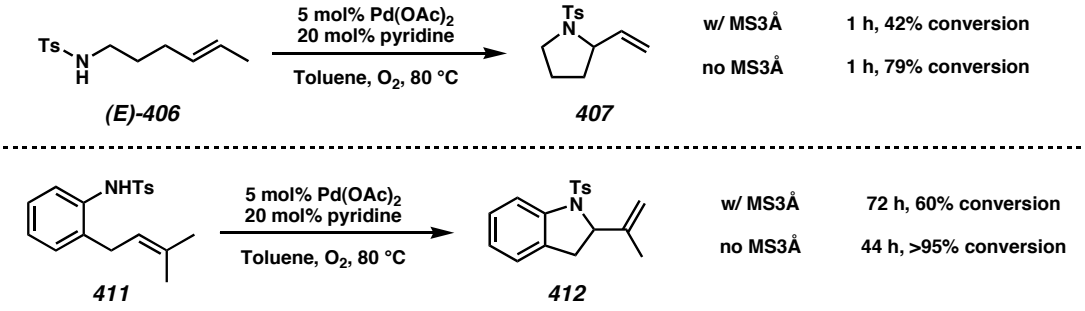
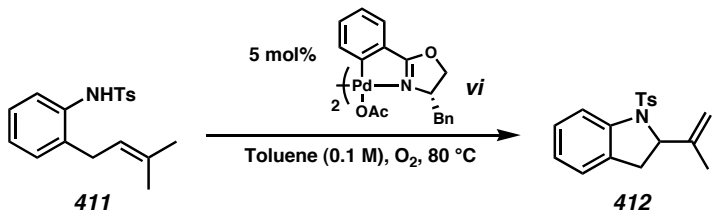
(13) Some of the reactions in this table are run without MS3Å. It was found during these reactions that added MS3Å provided no increased selectivity and in fact hindered reactivity in the cyclizations of tosylamides and tosylanilines.



(14) This observation was further validated by the oxidative cyclization with catalyst **vi**.



(15) Bisoxazoline **413** (entry 5) provided higher levels of conversion with the same degree of enantioselectivity; however, the synthetic difficulty of this ligand compared to bisoxazoline **391** thwarted its use in further studies.

(16) The palladium source had a dramatic effect on the reaction, $Pd(OAc)_2$ being the most effective precatalyst investigated. $Pd(TFA)_2$ resulted in a decrease in selectivity, while all other palladium sources were ineffective at catalyzing the transformation. See the experimental section for details.

(17) It is not clear if the deprotonation event occurs before or after nucleophilic attack on the activated olefin. It is believed, however, that deprotonation from an anilinium intermediate arising from the nucleophilic attack should be facile regardless of the nitrogen substituent.

(18) The synthetic difficulty of accessing these substrates (see Experimental Section) prevented us from further exploring these reactions.

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(20) This would be rather unsurprising. Nonligated palladium centers are more electron-deficient, likely increasing their reactivity toward olefin activation.

(21) (a) The aggregative decomposition occurs at palladium(0) and is therefore more prevalent in the Pd/DMSO/O_2 systems, where Pd(0) is the resting state for the catalyst. See, Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc*. **2002**, *124*, 766-767. (b) Pd(II) was found to be the resting state for the Pd/pyridyl/O_2 oxidation systems, which helps to prevent the same aggregative decomposition. See reference 19b. It is not clear what the resting state of the catalyst is in the bisoxazoline systems described herein.

(22) "N-H activation" is used figuratively in this explanation. A net N-H activation would most likely involve coordination of the nitrogen atom to the metal center followed by deprotonation of the cationic intermediate with concomitant loss of an acetate ligand.

(23) The latter scenario is less likely, but cannot be completely ruled out. No other olefin isomers were observed in the reaction mixture. Additionally, unpublished results by Raissa Trend and results by Hayashi et al. have shown that in the case of

oxygen atom nucleophiles, insertion of an olefin into a palladium-oxygen bond is the most likely mechanism. (a) Trend, R. M.; Stoltz, B. M. California Institute of Technology, Pasadena, CA. Unpublished work, 2005. (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc*. **2004**, *126*, 3036-3037.

(24) This model is not fully in agreement with every element of data. In particular, the reversal of enantioselectivity with pyridine-oxazoline **397** (Table 5.3.4, entry 6) is inconsistent with the enantioinduction model and cannot be rationalized at this time.

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