JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

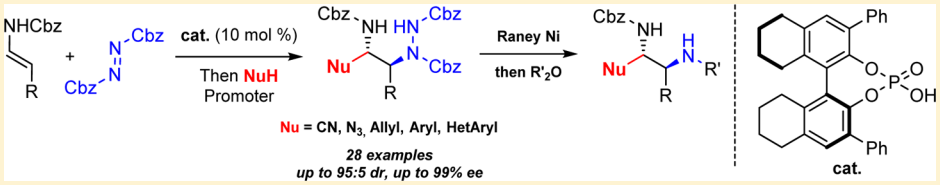
# Enantioselective Three-Component Amination of Enecarbamates Enables the Synthesis of Structurally Complex Small Molecules

Audrey Dumoulin,[†] Guillaume Bernadat,[‡] and Géraldine Masson*[,†]

[†]Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Université Paris-Sud, Université Paris-Saclay, 1 av. de la Terrasse, Gif-sur-Yvette 91198 Cedex, France

[‡]Équipe Molécules Fluorées et Chimie Thérapeutique, UMR-8076 (BioCIS), LabEx LERMIT, Faculté de Pharmacie, 5 Rue J.-B. Clément, Châtenay-Malabry92296 Cedex, France

Supporting Information

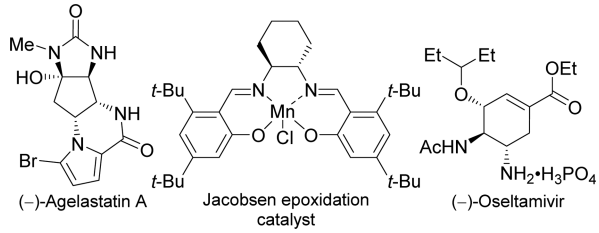



**ABSTRACT:** The control of asymmetric synthesis tools represents a major challenge, especially when it comes to the synthesis of bioactive molecules. In this context, the asymmetric synthesis of 1,2-diamines through amination of enecarbamates has been proposed as a highly efficient and tunable approach. Indeed, reactivity of the latter species could be exploited to realize a double functionalization via an electrophilic amination followed by nucleophilic trapping. Herein, we describe a chiral phosphoric acid catalyzed electrophilic amination of enecarbamates with dibenzyl azodicarboxylate and oxygenated or thiol-containing nucleophiles affording stable precursors of $\alpha$-hydrazinoimines in high yields and with almost complete enantioselectivities (up to >99%). These precursors were successfully functionalized with various silylated nucleophiles without epimerization of the stereogenic center, giving access to a wide range of 1,2-disubstituted 1,2-diamines. We also show that the thiolated precursors were successfully engaged in a Friedel–Crafts reaction against a variety of aromatic and heteroaromatic nucleophiles, leading to various 1-(hetero)aryl-1,2-diamines without loss of enantioselectivity and with complete diastereoselectivity. Reductive N–N bond cleavage provided the *N,N*-diprotected 1,2-diamines with no loss in diastereo- or enantioselectivity. The protocol was successfully scaled up to a multigram scale and the catalyst was successfully recovered, demonstrating the potential applications of this new methodology.

## INTRODUCTION

The 1,2-diamine scaffold is widely found in many biologically active compounds and synthetic pharmaceutical agents.[1] For instance, (−)-agelastatin A, isolated in 1993 by Pietra et al. from the marine sponge *Agelas dendromorpha*, has proved to be cytotoxic against human tumor cell lines.[2] (−)-Oseltamivir phosphate, also named Tamiflu, is an antiviral drug used in the treatment of influenza A and B.[3] Furthermore, 1,2-diamines are extensively employed in catalytic asymmetric reactions as chiral ligands (Scheme 1).[4] As a consequence, the development of an efficient enantioselective synthesis of 1,2-diamines has recently caught considerable attention.[5] Several routes toward such useful scaffolds have been reported, such as aza-Henry reaction,[6] aza-Michael addition reaction,[7] diamination of alkenes,[8] ring opening of meso-aziridines,[9] or reductive coupling of imines.[10] However, those methods have some limitations, such as, respectively, the requirement of an extra nitro group reduction step, the use of transition metals, a poor range of tolerated functional groups, and homocoupling side reactions. Over the past years, the electrophilic amination reaction[11] stood out as one of the most attractive routes to functionalize carbonyl compounds, but very few applications involving enamides or enecarbamates have been reported. In 2006, Kobayashi et al. described the first catalytic enantioselective amination of (*E*)-enecarbamates derived from acetophenone and catalyzed by a chiral diamine–$Cu^{II}$ complex (see Scheme 3a).[12] A few years later, Feng et al. disclosed an enantioselective amination of (*Z*)-$\alpha$-arylenamides using a chiral *N,N′*-dioxide–$Cu^{II}$ complex (see Scheme 3a).[13] Meanwhile, we reported an alternative approach via $\alpha$-amination of (*E*)-$\alpha$-

**Scheme 1. Selected Examples of 1,2-Diamines of Interest**



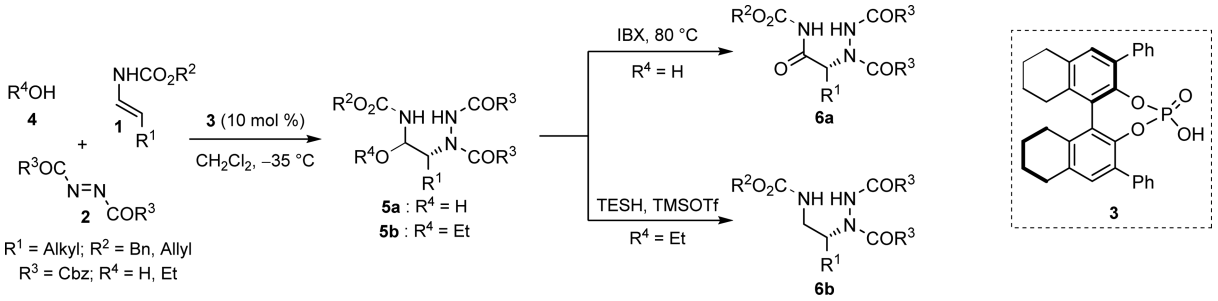

**Received:** December 30, 2016
**Published:** January 16, 2017



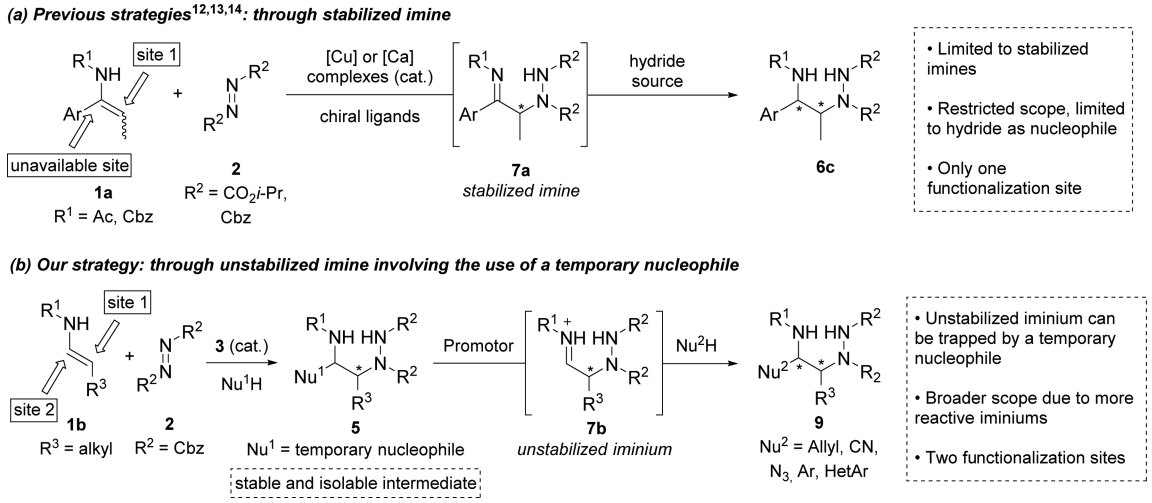


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775–1789

**Scheme 2. Our Previous Work on Catalytic Enantioselective Two-Step Amination of Enecarbamates: Amination/Oxidation or Amination/Reduction**




**Scheme 3. Comparison of Different Synthetic Strategies Starting from Enamide Derivatives**




arylenamides with chiral calcium bis(phosphate) complexes as catalysts.[14] These works provided robust routes to 1,2-diamines with complete diastereoselectivity starting from α-arylenamides. In this paper, we report the results of our efforts aiming at further expanding the scope of this chemistry in terms of suitable substrates while continuing to avoid degradation through hydrolysis, isomerization, or polymerization.[15] Indeed, we recently developed the first three-component direct amination of α-unsubstituted enecarbamates **1** with azodicarboxylates **2** and oxygenated nucleophiles **4** in the presence of a catalytic amount of chiral phosphoric acid **3**.[16] We hypothesized that fast enough trapping of the iminium intermediate with an appropriate nucleophile would prevent its degradation. New stable intermediate **5** arising from the trapping could then be engaged into further transformations.

The best candidates for playing the role of temporary nucleophiles proved to be alcohols and water.[17] As a result, this amination reaction afforded stable precursors of α-hydrazinoimines **5a** and **5b** (in good yields and with excellent enantioselectivities, up to >99% ee), which were oxidized or reduced, respectively, to α-amino acid precursors **6a** or vicinal diamines **6b** (Scheme 2). Importantly, the mild reaction conditions were compatible with a range of functional groups on enecarbamates such as protected alcohols, linear alkyl groups, cyclopropyl groups, and double and triple bonds. In light of our previous investigations regarding the field of asymmetric organocatalysis with particular emphasis on the reactivity of enamides,[18] we aimed at further enlarging the field of accessible 1,2-disubstituted 1,2-diamines. In order to develop a novel method for the enantioselective synthesis of libraries of complex small molecules with high levels of scaffold diversity, we first concentrated our efforts on trapping the regenerated iminium ion with a wide variety of nucleophiles. For the whole process to be successful, an alternative approach had to be found. Indeed, in order to avoid epimerization of the previously formed stereogenic center, iminium **7b** had to be trapped as fast as possible, implying the use of Lewis or Brønsted acids to accelerate the nucleophilic addition. Moreover, the iminium intermediate had to be regenerated under soft conditions to prevent its degradation (Scheme 3b). Herein, we report a highly enantioselective three-component electrophilic amination of enecarbamates with azodicarboxylates and alcohols by trapping the iminium ion with silylated nucleophiles.[16] We also broadened this strategy by combining the catalytic three-component amination reaction of enecarbamates and a subsequent Friedel−Crafts reaction with a wide range of heterocycles.

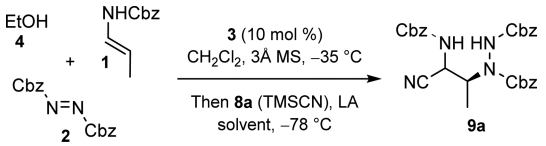
## RESULTS AND DISCUSSION

In our previous work,[16] we have demonstrated that the enantioselective three-component amination of enecarbamates with diazocarboxylates and oxygenated nucleophiles can provide the *N*-carbamoylamino ether intermediate **5b** in which no epimerization is observed. Thus, we envisaged that the same strategy could be extended to diversely substituted silylated nucleophiles. We initiated our investigation by exploring the reaction of *N*-carbamoylamino ether **5b** with trimethylsilyl cyanide **8a** and trimethylsilyl trifluoromethanesul-


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

fonate in acetonitrile at −78 °C. We were delighted to find that desired product **9a** could be obtained in 77% yield without enantioselectivity loss. The best Lewis acid source was found to be boron trifluoride diethyl etherate. Finally, the yield was increased to 82% by changing the solvent from acetonitrile to dichloromethane (Table 1). With those optimized conditions

**Table 1. Survey of Reaction Conditions for the Two-Step Reaction Sequence: Amination/Nucleophilic Addition of Silylated Compounds**[a]

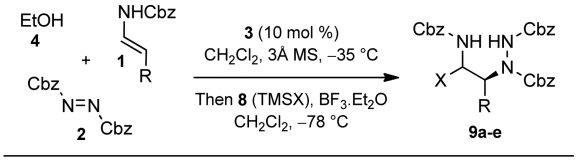


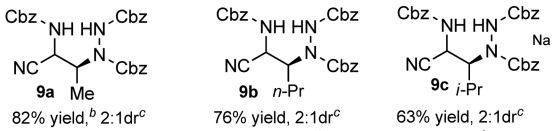

| entry | Lewis acid | solvent | yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|
| 1 | TMSOTf | $CH_3CN$ | 77 | 92/94 |
| 2 | TMSOTf | $CH_2Cl_2$ | 63 | 90/95 |
| 3 | BF3.Et2O | $CH_2Cl_2$ | 82 | 98/96 |

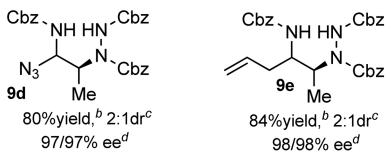
[a]General conditions: enecarbamate **1** (0.10 mmol), dibenzyl azodicarboxylate (0.15 mmol), ethanol (0.10 mmol), 3 Å molecular sieves (25 mg), catalyst derived from octahydro-(*S*)-BINOL 3 (0.01 mmol) in $CH_2Cl_2$ (1.0 mL) at −35 °C for 16 h. [b]Yields refer to chromatographically pure products. [c]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. [d]2:1 ratio of diastereomers.

in hands, the scope of this asymmetric $\alpha$-amination/nucleophilic addition sequence was investigated (Table 2). A range of silylated nucleophiles, such as TMSCN, $TMSN_3$, and allyltrimethylsilane, gave the corresponding products, opening the way to numerous synthetic options. More hindered $\beta$-substituted enecarbamates **1b** and **1c**, bearing, respectively,

**Table 2. Substrate Scope of the Enantioselective Phosphoric Acid-Catalyzed Sequential Synthesis of 1,2-Diamines with Silylated Nucleophiles**[a]



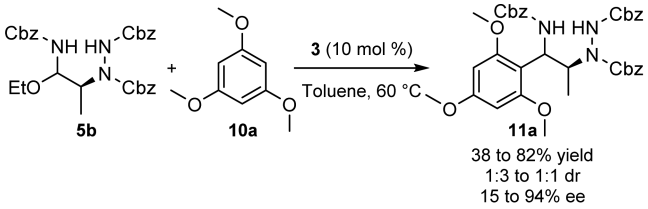



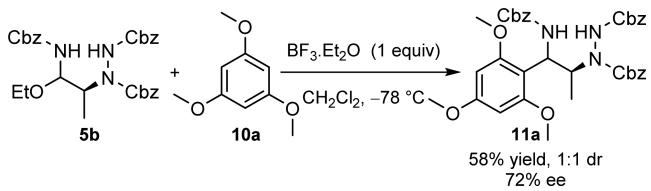

[a]General conditions: enecarbamate **1** (0.10 mmol), dibenzyl azodicarboxylate (0.15 mmol), ethanol (0.10 mmol), 3 Å molecular sieves (25 mg), and (*S*)-**3** in $CH_2Cl_2$ (1.0 mL) at −35 °C for 16 h. Then **8** (0.15 mmol) and $BF_3{\cdot}Et_2O$ (0.15 mmol) in $CH_2Cl_2$ (0.3 mL) at −78 °C for 2 h. [b]Yields refer to chromatographically pure products. [c]dr determined by $^1H$ NMR analysis of crude mixtures. [d]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

linear or branched alkyl chains, also afforded the desired product with good yield and enantioselectivities.

Encouraged by these results, we envisaged expanding this strategy with the use of other nucleophiles such as aromatic and heteroaromatic which are useful building blocks in biologically active compounds,[19] whether in the agrochemical,[20] pharmaceutical,[21] or cosmetics field.[22] The past decades have seen the development of asymmetric Friedel−Crafts reactions with various imines as one of the most powerful tools to access enantioenriched 2-substituted aryl or heteroaryl derivatives.[23] Despite these advances, most of the reactions described rely on aromatic imines. In the case of aliphatic reactions, the reaction generally leads to poorer enantioselectivities and moderate yields,[24] given the fact that the latter species tend to isomerize into corresponding enamines. Thus, there are very few examples[25] with aliphatic imines, rendering the application of asymmetric Friedel−Crafts reaction to our substrates more challenging. To begin our study, we elected *N*-carbamoylamino ether intermediate **5b** as the iminium precursor. In considering possible isomerization of the previously formed stereogenic center, we decided to heat the reaction medium in the presence of a chiral phosphoric acid, hoping that Brønsted acid-catalyzed Friedel−Crafts reaction would occur faster than epimerization. Unfortunately, our first attempts in toluene at 60 °C gave contrasting results because yields and enantiomeric excesses were not reproducible (Scheme 4). A similar result was

**Scheme 4. First Attempt for the Chiral Phosphoric Acid-Catalyzed Asymmetric Friedel−Crafts Reaction of Indole with Iminium Precursor 5b**



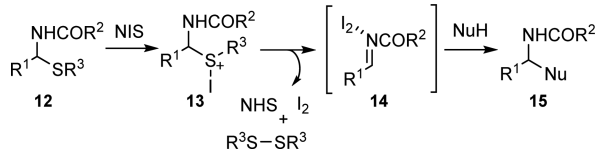

obtained when the reaction was carried out at −78 °C in the presence of 1 equiv of $BF_3{\cdot}Et_2O$. As we suspected, the acidic conditions of the reaction mixture indeed promoted the iminium epimerization and hydrolysis.

To overcome this problem, it was essential to produce the iminium intermediate **7b** under milder conditions as well as accelerate the rate of addition of nucleophilic aromatic ring. Recent works in our group revealed that *N*-acyliminium ions can be efficiently generated from $\alpha$-amidosulfides[17b,26] in the presence of stoichiometric or catalytic amounts of *N*-iodosuccinimide (NIS) and proceed through an aza-Friedel−Crafts reaction with arene nucleophiles.[27] This strategy relies on the formation of cationic amidoiodosulfonium intermediate **13**, possessing a better leaving group to generate the iminium species under soft conditions (Scheme 5). One of the main advantages of this strategy relies on the use of NIS to generate the imine under acid/base-free conditions. Additionally,



DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

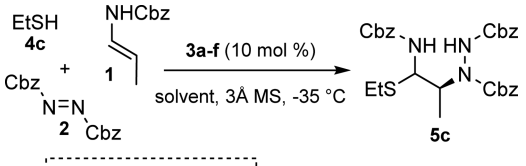
**Scheme 5. Plausible Reaction Mechanism of the NIS-Catalyzed Aza-Friedel–Crafts Reaction**

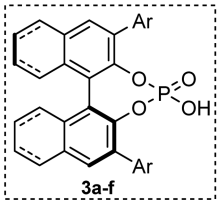



electrophilicity of the latter species could be increased by the Lewis acid character of in situ generated iodine upon coordination therewith (Scheme 5).

On the basis of this work, we started to optimize the synthesis of the *N*-carbamoylamino thioether **5c** as our new imine precursor. We first examined the reaction of (*E*)-*N*-(benzyl prop-1-en-1-yl)carbamate **1**, dibenzyl azodicarboxylate **2**, ethanethiol **4**, and 10 mol % of chiral phosphoric acid catalyst **3** in the presence of 3 Å molecular sieves in dichloromethane at −35 °C (Table 3). To our delight, the desired product was

**Table 3. Optimization of the Synthesis of *N*-Carbamoylaminothioether 6b[a]**




Ar = $C_6H_5$ (**3a**)
Ar = 2-Napht (**3b**)
Ar = Phenantr (**3c**)
Ar = $SiPh_3$ (**3d**)
Ar = 2,4,6-(*i*Pr)$_3C_6H_2$ (**3e**)
Ar = $C_6H_5$ (**3f**)

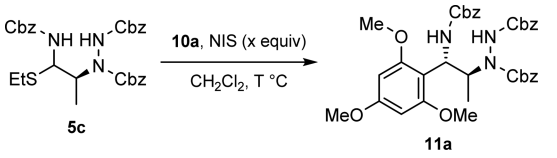
| entry | 3 | solvent | yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|
| 1 | **3a** | $CH_2Cl_2$ | 96 | 91/91 |
| 2 | **3b** | $CH_2Cl_2$ | 91 | 88/91 |
| 3 | **3c** | $CH_2Cl_2$ | 64 | 25/26 |
| 4 | **3d** | $CH_2Cl_2$ | 58 | <5 |
| 5 | **3e** | $CH_2Cl_2$ | 21 | 60/64 |
| 6 | **3f**[e] | $CH_2Cl_2$ | 99 | 96/90 |
| 7 | **3f**[e] | toluene | 98 | 85/80[f] |
| 8 | **3f**[e] | THF | 23 | ND |
| 9 | **3f**[e] | $CH_2Cl_2$ | 99[g] | 99/98[g] |

[a]General conditions: enecarbamate **1** (0.10 mmol), dibenzyl azodicarboxylate (0.15 mmol), ethanethiol (0.10 mmol), 3 Å molecular sieves (25 mg), and (*S*)-**3** in $CH_2Cl_2$ (1.0 mL) at −45 °C for 16 h. [b]Yields refer to chromatographically pure products. [c]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. [d]2:1 ratio of separable diastereomers. [e]Derived from octahydro-(*S*)-BINOL. [f]dr = 1:19. [g]At −45 °C.

obtained in 96% yield and with excellent enantioselectivities for each diastereomer couple. Among the two stereogenic centers created, only the one at the α-position was controlled, which is not a problem since the other will be discarded upon imine regeneration during the following step. The catalytic efficiencies of some chiral phosphoric acids were tested (entries 1–6). (*S*)-$H_8$-3,3′-bis-phenyl–BINOL phosphoric acid **3f** proved to be the best catalyst in terms of yields and enantioselectivities. A rapid screening of solvents (entries 6–8) showed that dichloromethane remained the best solvent for this reaction. Finally, lowering the temperature to −45 °C allowed the reaction to proceed with higher enantioselectivities (entry 9).

We next turned our attention to the development of the NIS-assisted Friedel–Crafts reaction (Table 4). For this optimiza-

**Table 4. Survey of Reaction Conditions for the NIS-Assisted Friedel–Crafts Reaction with 1,3,5-Trimethoxybenzene[a]**



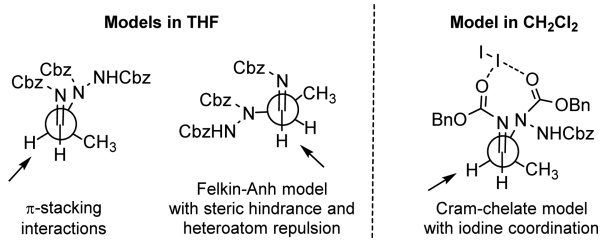

| entry | NIS (equiv) | *T* (°C) | yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|
| 1 | 1.1 | −78 | 36[e] | 89[e] |
| 2 | 1.1 | −30 | 54[e] | 91[e] |
| 3 | 0.5 | −30 | 74[e] | 97[e] |
| 4 | 0.5 | 0 | 85[f] (84[g]) | 96[f] (97[g]) |
| 5 | 0.3 | 0 | 89[f] (77[e]) | >99[f] (97[e]) |
| 6 | 0.3 | rt | 77[f] | 92[f] |
| 7 | 0.1 | 0 | 76[f] | 95[f] |
| 8 | 0.3 | 0 | 34[f,h,i] | ND[i] |

[a]General conditions: α-amido sulfide **6b** (0.10 mmol), 1,3,5-trimethoxybenzene (0.11 mmol), and NIS in CH2Cl2 for 1 h. [b]Yields refer to chromatographically pure products. [c]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. [d]dr > 95:5. [e]Concentration 0.1 mol/L. [f]Concentration 0.05 mol/L. [g]Reaction conducted with $I_2$ instead of NIS. [h]dr = 1:1. [i]In THF.

tion, 1,3,5-trimethoxybenzene **10a** was selected as the model arene nucleophile substrate. We initially performed the reaction by using α-amidosulfide **5c** and arene **10a** with a stoichiometric amount of NIS at −78 °C in $CH_2Cl_2$. To our great surprise, the desired product under the form of a single diastereoisomer was obtained in only 5 min with 36% yield and an encouraging enantioselectivity of 91% (entry 1). However, two side products were also isolated, corresponding to the iodinated 1,3,5-trimethoxybenzene and resulting from enamine–imine tautomerization. These results suggest that the Friedel–Crafts reaction does not proceed fast enough at −78 °C, and conversely, the imine is produced too quickly. To favor nucleophilic addition of **10a**, the temperature was raised to −30 °C, and the amount of NIS was revised downward (entries 2 and 3). The desired Friedel–Crafts product **11** was finally obtained without side product at 0 °C with 30 mol % of NIS (entry 5). Further attempts to decrease the amount of NIS resulted in a diminution of the yield (entry 7). Surprisingly, we found that running the reaction in a chelating and slightly polar solvent, such as THF, leads to a complete loss of diastereoselectivity (entry 8). To rationalize this, we postulated a transition state in which in situ generated iodine could act as a Lewis acid according to the Cram chelate model (Scheme 6). π-Stacking could also play a role in promoting the diastereoselective pathway. On the contrary, when the reaction is performed in THF, this coordinating solvent could interfere between iodine and the imine intermediate.[28] Logically, this would have two consequences: first, a decrease of the iminium reactivity, leading to the observed lower yield (34%), and second, a competition between the Felkin–Anh model governed by electronic repulsions and the model ruled by π-stacking. This interpretation is consistent with the absolute configuration, which was unambiguously determined by an X-


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775–1789

**Scheme 6. Postulated Intermediate Depending on the Solvent for the Diastereoselective NIS-Assisted Friedel–Crafts Reaction**

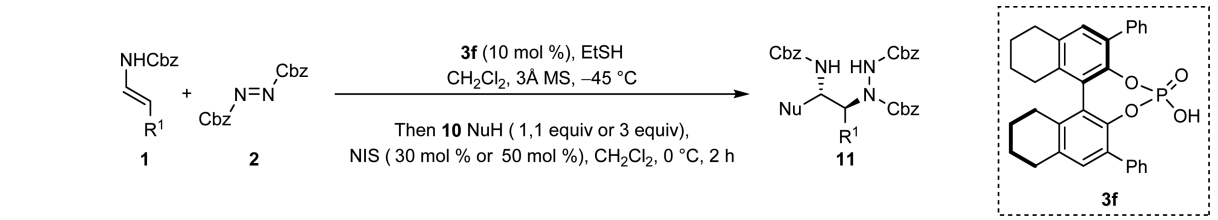


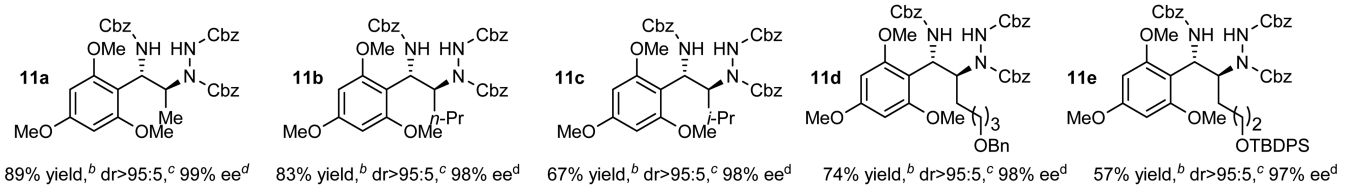

ray crystal structure analysis of deprotected product **13a** (cf. the Supporting Information).

At this stage, we started an assessment of the scope of the reaction with 1,3,5-trimethoxybenzene (Table 5). A wide range of enecarbamates bearing aliphatic as well as branched alkyl chains provided the desired 1,2-diamine products in good yields and with excellent enantioselectivities (from 97 to 99% ee) as well as complete syn/anti selectivity (>95:5, compounds **11a–f**). To evaluate the tolerance of the reaction toward diverse functional groups, a variety of *β*-substituted enecarbamates **1** was tested. To our delight, the benzyl and *tert*-butyldiphenylsilyl-protected alcohols yielded **11d** and **11e** with very high enantioselectivities. The presence of a terpene motif (such as those extensively found in natural products) was tolerated as well.[29] We next aimed at further enlarging the scope of arenes compatible with this reaction by testing some commonly used heterocyclic compounds (Table 5). Surprisingly, heterocycles such as indazole, pyrrazole, 1,3-dimethoxybenzene, and furan, which are notably less nucleophilic substrates according to Mayr's scale,[30] led to a mixture of diastereomers (2:1 ratio). Such a result could be explained by different steric properties between **10a** and the other arenes, which are particularly less hindered. Nevertheless, in each case, heterocycles were converted into the corresponding products with excellent enantioselectivities for both diastereomer couples. The reaction with indole **10k** (which was expected to occur identically) did not produce the same mixture of diastereomers but bis-addition product **12a** with a very good yield and 99% ee (Table 6).[23a,c,31] This observation suggests that, in this instance, electron-rich indole **10k** would be nucleophilic enough to further react through a second Friedel–Crafts addition to **11k** with the assistance of iodine playing the role of Lewis acid and being regenerated during the catalytic process (Scheme 7). This phenomenon is well-known for being an attractive way to synthesize bis(indolyl)methane derivatives.[32] Moreover, it increases in worth since bis(indolyl)methane are powerful antibiotics and anti-inflammatory agents.[33]

Driven by this interesting result, we decided to evaluate the potential of this reactivity with various indoles (Table 6). As we hoped, indoles bearing electron-withdrawing substituents, such as Br, $NO_2$, CN, and $CO_2Me$, underwent the expected double aza-Friedel–Crafts reaction, leading to the corresponding bisindole **12b–f** products with good-to-high yields and excellent enantioselectivities (98–99% e.e.). However, electron-rich substrates, such as 5-OMe derivatives, generated a mixture of separable double- and monoaddition products **12g** and **11k** with an excellent enantioselectivity. Importantly, an almost complete syn diastereoselectivity was observed in the formation of **11k**. Attempts to afford selectively one of the two

**Table 5. Substrate Scope of the Enantioselective Phosphoric Acid-Catalyzed Sequential Synthesis of 1,2-Diamines with Heterocycles**[a]




89% yield,[b] dr>95:5,[c] 99% ee[d] | 83% yield,[b] dr>95:5,[c] 98% ee[d] | 67% yield,[b] dr>95:5,[c] 98% ee[d] | 74% yield,[b] dr>95:5,[c] 98% ee[d] | 57% yield,[b] dr>95:5,[c] 97% ee[d]

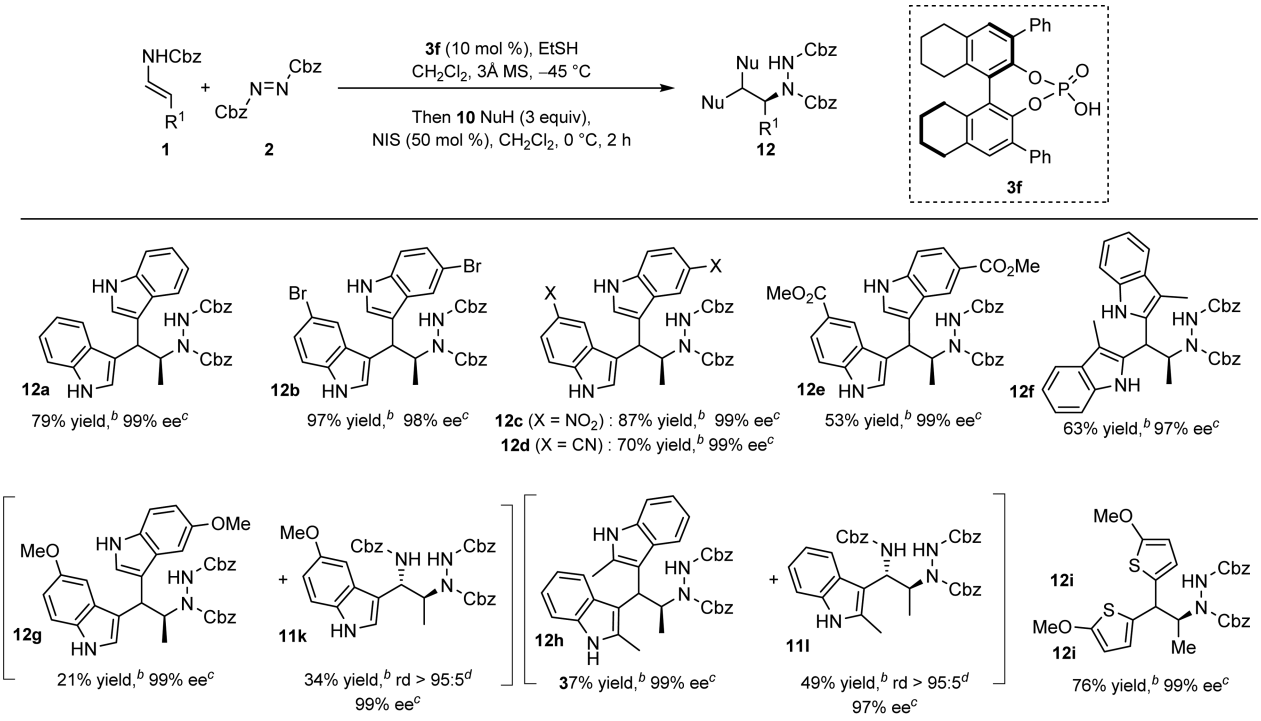
67% yield,[b] dr>95:5,[c] 98% ee[c] | 73% yield,[b] dr 2:1,[c] 99/97% ee[d] | 57% yield,[b] dr 2:1,[c] 97/94% ee[d] | 64% yield,[b]dr 2:1,[c] 99/89% ee[d] | 72% yield,[b] dr 2:1,[c] 98/93% ee[c]

[a]General conditions: enecarbamate **1** (0.10 mmol), dibenzylazodicarboxylate (0.15 mmol), ethanethiol (0.10 mmol), 3 Å molecular sieve (25 mg), and (*S*)-**3f** in $CH_2Cl_2$ (1.0 mL) at −45 °C for 16 h. Then **10** (0.11 mmol) and NIS (0.03 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C for 2 h. [b]Yields refer to chromatographically pure products. [c]dr determined by $^1$H NMR analysis of crude mixtures. [d]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase.



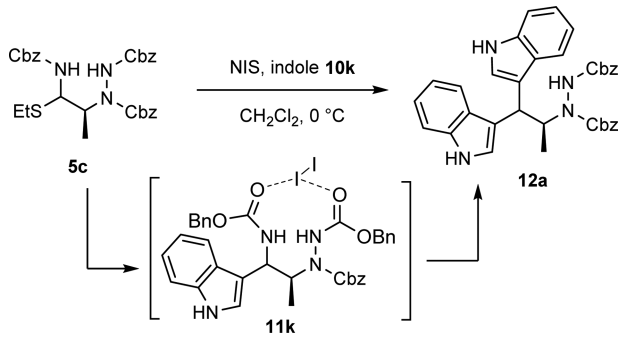
DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775–1789

**Table 6. Substrate Scope of the Enantioselective Phosphoric Acid-Catalyzed Sequential Synthesis of 1,2-Diamines with Indoles**[a]




[a]General conditions: enecarbamate **1** (0.10 mmol), dibenzyl azodicarboxylate (0.15 mmol), ethanethiol (0.10 mmol), 3 Å molecular sieves (25 mg), and (*S*)-**3f** in $CH_2Cl_2$ (1.0 mL) at −45 °C for 16 h. Then **10** (0.3 mmol) and NIS (0.05 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C for 2 h. [b]Yields refer to chromatographically pure products. [c]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase. [d]dr determined by $^1$H NMR analysis of crude mixtures.

**Scheme 7. Plausible Reaction Mechanism**

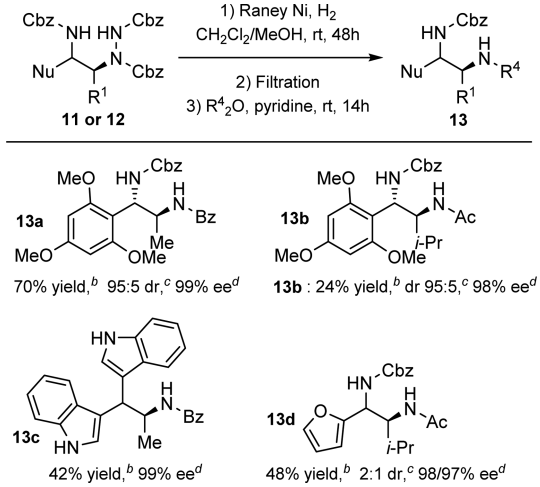



products have not been successful so far. A similar result was obtained with 2-methylindole furnishing double- and mono-*N*-alkylated products **12h** and **11l** with a high enantioselectivity. Finally, we also performed the sequential reactions with the 2-methoxythiophene and obtained bis-alkylated products **12i** in good yield and with an equally good enantioselectivity.

To increase chemical diversity accessible through this method, the hydrazine bond was cleaved in the presence of Raney nickel, and the free amine was diversely protected, affording the desired 1,2-diamines without epimerization of the stereogenic center (Table 7).

Next, we explored the synthetic versatility of the 1,2-diamines by derivatization of the furan ring to enantioenriched dihydropyridone (Scheme 8). Since the dihydropyridone is a common building block in the synthesis of various natural products,[34] this represents a new entry to synthetic precursors of nitrogen-containing complex heterocycles. Indeed, the aza-

**Table 7. Hydrogenation of the Hydrazine Group and Protection**[a]



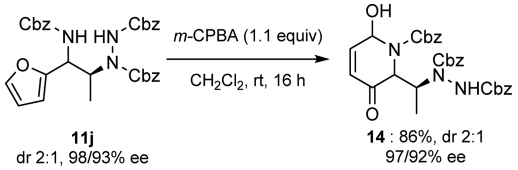

[a]General conditions: **11** (1.0 equiv), $H_2$ ($P$ = 4 bar), and Raney Ni in $CH_2Cl_2$/MeOH = 9/1 ($C$ = 0.1 M) at rt for 48 h. After filtration, the mixture was dissolved in pyridine ($C$ = 0.1 M) with $R^4{}_2O$ (5.0 equiv) for 12 h. [b]Yields refer to chromatographically pure products. [c]dr determined by $^1$H NMR analysis of crude mixtures. [d]Enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

Achmatowicz oxidation[35] of furyl carbamate **11j** as a mixture of diastereomers (98/93% ee) rearranged to the corresponding enantioenriched dihydropyridone **14** in 95% yield without any loss of enantiomeric excess (97/92% ee).



DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

**Scheme 8. Synthesis of Dihydropyridone Derivative via Aza-Achmatowicz Reaction**




**11j**
dr 2:1, 98/93% ee

**14** : 86%, dr 2:1
97/92% ee

Finally, to demonstrate the robustness of our work, a multigram-scale reaction was performed. Product **11a** (2.64 g) was synthesized from 1.0 g of enecarbamates with 76% yield and 99% enantiomeric excess. Moreover, it is worth noting that the phosphoric acid catalyst was totally recovered during the column chromatography, allowing us to recycle it and to reuse it for another reaction.

## CONCLUSION

In conclusion, we report in this paper a selective, easy, and rapid-to-implement procedure for the synthesis of 1,2-diamines. Our protocol relies on a temporary nucleophile-based strategy to control reactivity of the key imine intermediate. Its synthetic utility was demonstrated by the preparation of a wide range of complex (notably heterocyclic) derivatives in an expeditious and fully enantioselective manner. Under appropriate activation conditions, double Friedel−Crafts adducts can also be obtained, which further expands the application field of this method.

## EXPERIMENTAL SECTION

**Materials and General Methods.** All reactions requiring anhydrous conditions or inert atmosphere were carried out under argon atmosphere in dried glassware. Immersion coolers IMC-40 and TC100E fitted with a probe and a flexible cooling tube were used to perform slow reactions at low temperature. Solvents were distilled by standard methods using the appropriate drying agent and stored over molecular sieves under argon. All other reagents were obtained from commercial suppliers unless otherwise noted. Flash column chromatography was carried out using 40−63 $\mu$m particle sized silica gel with air pressure. Analytical thin-layer chromatography (TLC) plates (silica gel 60 F254) were visualized either with a UV lamp (254 nm) or by submersion in potassium permanganate, ninhydrine, or iodine. Melting points were recorded using a melting point apparatus (Büchi B-540) and are uncorrected. Specific rotations for chiral compounds were recorded on a PerkinElmer 141 using sodium D ray (589 nm) at room temperature in a 700-$\mu$L cell with a path length of 1 dm in deuterochloroform. Infrared spectra were recorded on a PerkinElmer Spectrum BX FT-IR spectrometer, and the characteristic IR absorption frequencies are reported in $cm^{-1}$. Proton NMR ($^1H$) spectra were recorded on a Bruker Avance 600, 500, or 300 MHz instrument, and carbon NMR ($^{13}C$) spectra were recorded at 75 MHz. Some NMR measurements were performed at 70 or −30 °C to minimize signal broadening due to the rotamer mixture. NMR experiments were carried out in deuterochloroform ($CDCl_3$) or in trideuteroacetonitrile ($CD_3CN$). Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to residual solvent as an internal reference ($^1H$: 7.26, $^{13}C$: 77.16 ppm for $CHCl_3$ and $^1H$: 1.94, $^{13}C$: 1.32 ppm for $CD_3CN$). The following abbreviations are used for the multiplicities: s: singlet; d: doublet; t: triplet; q: quadruplet; quint: quintuplet; m: multiplet or overlap of nonequivalent resonances; br s: broad singlet; app: apparent; rot: rotamer. Coupling constants ($J$) are reported in hertz (Hz). Mass spectra were obtained from a MALDI-TOF type instrument for the high-resolution mass spectra. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) or supercritical fluid chromatogroaphy (SFC) equipped with diode array UV detectors using Chiralpak AD-H, OD-H, AS-H, OJ-H, IA, and IB columns. Enecarbamate starting materials were prepared according to the literature procedure.[36] Catalysts **3** were prepared according to literature procedures.[37]

**General Procedure for the Enantioselective Synthesis of Cyano-, Azido-, or Allyl-Substituted Vicinal Diamines.** Under argon, the *E*-enecarbamate (0.1 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (0.4 mL) in a flame-dried flask containing activated powdered 3 Å molecular sieves. The solution was stirred at room temperature for 10 min before being cooled to −35 °C and stirred for additional 10 min. Dibenzyl azodicarboxylate (44.7 mg, 0.15 mmol, 1.5 equiv) dissolved in $CH_2Cl_2$ (0.3 mL) was added, and the reaction mixture was stirred for 10 min. Then EtOH (5.9 $\mu$L, 0.1 mmol, 1.0 equiv) and finally the (*S*)-phosphoric acid (5.0 mg, 0.01 mmol, 0.1 equiv) in $CH_2Cl_2$ (0.3 mL) were added, and the reaction mixture was stirred for 16 h at −35 °C. Solvent was removed under reduced pressure, and the residue was purified over silica gel (heptane/EtOAc 6/4).

The obtained product was dissolved in $CH_2Cl_2$ (0.3 mL) and cooled to −78 °C. Then TMSCN (20 $\mu$L 0.15 mmol, 1.5 equiv) and $BF_3{\cdot}Et_2O$ (20 $\mu$L 0.15 mmol, 1.5 equiv) were successively added, and the reaction mixture was stirred at −78 °C for 2 h. The mixture was quenched with an aqueous solution of $NaHCO_3$ and allowed to reach room temperature. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (heptane/EtOAc 6/4) to afford the desired compound.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-cyanopropyl]carbamate (**9a**).* Compound **9a** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (42.4 mg, dr 1:1) in 82% yield: $[\alpha]^{23}_D$ −7.2 (*c* 1.0, $CHCl_3$); IR 3300, 3034, 1702, 1498, 1455, 1406, 1292, 1220, 1152, 1004, 911, 736, 696 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.56 (br s, 0.6H, rot.1, NH), 7.42−7.29 (m, 15H), 7.20 (br s, 0.4H, rot.2, NH), 6.71 (br s, 0.4H, rot.1, NH), 6.31 (br s, 0.6H, rot.2, NH), 5.21−5.05 (m, 6H), 4.77 (dq, app t, $J$ = 7.5 Hz, 0.6H, rot.1), 4.70 (d, app q, $J$ = 7.0 Hz, 0.6H, rot.1), 4.64 (d, app q, $J$ = 7.0 Hz, 0.4 Hz, rot.2), 4.57 (dq, app t, $J$ = 8.5 Hz, 0.4H, rot.2), 1.36 (d, $J$ = 6.5 Hz, 1.3H, rot.1), 1.29 (d, $J$ = 7.0 Hz, 1.7H, rot.2); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of diastereomers and rotamers: 156.6/156.5 (Cq, rot.1/rot.2), 156.4/156.3 (Cq, rot.1/rot.2), 156.2/156.1 (Cq, rot.1/rot.2), 137.5/137.4 (Cq, rot.1/rot.2), 137.1 (Cq), 136.9 (Cq), 129.6 (2 × CH), 129.5 (2 × CH), 129.4 (2 × CH), 129.3 (CH), 129.2 (2 × CH), 129.1 (2 × CH), 129.0 (CH), 128.9 (2 × CH), 128.6 (CH), 118.2 (Cq), 69.0/68.9 ($CH_2$, rot.1/rot.2), 68.8/68.4 ($CH_2$, rot.1/rot.2), 68.0 ($CH_2$), 55.3/54.9 (CH, rot.1/rot.2), 46.5/46.3 (CH, rot.1/rot.2), 14.9/14.7 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{28}H_{29}N_4O_6$ $[M + H]^+$ 517.2082, found 517.2089. Enantiomeric excess is 98/96% determined by HPLC (Chiralpak AD-H, heptane/*i*PrOH = 95/5, flow rate = 1.0 mL/min, 214 nm): Major diastereomer: minor isomer, $t_R$ = 70.3 min; major isomer, $t_R$ = 73.2 min. Minor diastereomer: major isomer, $t_R$ = 94.9 min; minor isomer, $t_R$ = 112.0 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-cyanopentyl]carbamate (**9b**).* Compound **9b** was obtained from the corresponding *E*-enecarbamate (**1b**, 21.9 mg, 0.1 mmol) as a colorless oil (41.4 mg, dr 1:1) in 76% yield: $[\alpha]^{23}_D$ −2.3 (*c* 1.0, $CHCl_3$); IR 3293, 3034, 2961, 1721, 1514, 1260, 1226, 745, 697 $cm^{-1}$; $^1H$ NMR (600 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 8.23 (br s, 0.6H, rot.1, NH), 8.12 (br s, 0.3H, rot.2, NH), 8.03 (br s, 0.1H, rot.3, NH), 7.68−7.17 (m, 15H), 7.17−6.62 (m, 1H, NH), 5.33−4.96 (m, 6H), 4.96−4.24 (m, 2H), 1.71−1.52 (m, 1H), 1.52−1.40 (m, 1H), 1.40−1.27 (m, 1H), 1.27−1.14 (m, 1H), 0.88 (t, $J$ = 6.6 Hz, 1.8H, rot.1), 0.85 (t, $J$ = 6.6 Hz, 1.2H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 156.5 (Cq), 156.2/156.0 (Cq, rot.1/rot.2), 155.6 (Cq), 136.9 (Cq), 136.7/136.5 (Cq, rot.1/rot.2), 136.3/136.2 (Cq, rot.1/rot.2), 129.3 (2 × CH), 129.2 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 128.7 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.1 (2 × CH), 117.7 (Cq), 68.9/68.7 ($CH_2$, rot.1/rot.2), 68.4 ($CH_2$), 67.7/67.3 ($CH_2$, rot.1/rot.2), 58.3/57.3/57.0 (CH, rot.1/rot.2/rot.3), 45.7/45.3/44.8 (CH, rot.1/rot.2/rot.3), 30.8/30.6


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

($CH_2$, rot.1/rot.2), 19.8/19.2 ($CH_2$, rot.1/rot.2), 13.6 ($CH_3$); ESI-HRMS calcd for $C_{30}H_{32}N_4O_6Na$ $[M + Na]^+$ 567.2214, found 567.2222. Enantiomeric excess is 91/90% determined by HPLC (Chiralpak IC, heptane/*i*PrOH = 90/10, flow rate = 0.8 mL/min, 214 nm). Major diastereomer: major isomer, $t_R$ = 18.6 min; minor isomer, $t_R$ = 27.1 min. Minor diastereomer: major isomer, $t_R$ = 24.8 min; minor isomer, $t_R$ = 32.3 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-cyano-3-methylbutyl]carbamate (**9c**).* Compound **9c** was obtained from the corresponding *E*-enecarbamate (**1c**, 21.9 mg, 0.1 mmol) as a colorless oil (34.3 mg, dr 1:2) in 63% yield: $[\alpha]^{23}_D$ +15.4 (*c* 0.5, $CHCl_3$); IR 3287, 2967, 1698, 1517, 1306, 1233, 739, 696 $cm^{-1}$; $^1H$ NMR (600 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.48−7.12 (m, 15H), 6.51 (br s, 0.5H, rot.1, NH), 6.47 (br s, 0.5H, rot.2, NH), 5.34−4.93 (m, 6H), 4.23 (d, app dd, *J* = 5.1 Hz and *J* = 11.1 Hz, 1H), 3.98 (dq, app dd, *J* = 5.1 Hz and *J* = 10.5 Hz, 1H), 2.34−2.21 (m, 0.3H, rot.1), 2.21−2.01 (m, 0.7H, rot.2), 1.09 (d, app dd, *J* = 6.6 Hz and *J* = 12.0 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 1.5H, rot.1), 0.81 (d, *J* = 6.6 Hz, 1.5H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 159.5 (Cq), 156.5 (Cq), 155.6 (Cq), 136.9 (Cq), 136.7 (Cq), 136.3 (Cq), 129.3 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.9 (2 × CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 117.3 (Cq), 68.9/68.7 ($CH_2$, rot.1/rot.2), 68.5/68.4 ($CH_2$, rot.1/rot.2), 67.8/67.7 ($CH_2$, rot.1/rot.2), 64.5/63.1 (CH, rot.1/rot.2), 43.0/42.9 (CH, rot.1/rot.2), 28.4/28.2 (CH, rot.1/rot.2), 19.8/19.6 ($CH_3$, rot.1/rot.2), 18.4/18.3 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{30}H_{32}N_4O_6Na$ $[M + Na]^+$ 567.2214, found 567.2236. Enantiomeric excess is 58/47% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: major isomer, $t_R$ = 32.8 min; minor isomer, $t_R$ = 100.9 min. Minor diastereomer: minor isomer, $t_R$ = 69.9 min; major isomer, $t_R$ = 75.6 min.

*Benzyl N-[(2S)-1-Azido-2-{[(benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}propyl]carbamate (**9d**).* Compound **9d** was obtained from the corresponding *E*-enecarbamate (**1a**, 21.9 mg, 0.1 mmol) as a colorless oil (42.6 mg, dr 1:2) in 80% yield: $[\alpha]^{23}_D$ +6.0 (*c* 1.0, $CHCl_3$); IR 3295, 3034, 2106, 1695, 1514, 1454, 1408, 1215, 1060, 1019, 911, 778, 734, 694 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.42−7.27 (m, 15H), 6.56 (br s, 1H, NH), 5.44−5.28 (m, 0.6H, dia.1), 5.28−5.21 (m, 0.4H, dia.2), 5.21−5.06 (m, 6H), 4.43 (dq, app q, *J* = 7.0 Hz, 0.6H, dia.1), 4.16 (dq, app q, *J* = 7.5 Hz, 0.4H, dia.2), 1.28 (d, *J* = 6.5 Hz, 2H, rot.1), 1.20 (d, *J* = 6.5 Hz, 1H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 158.6/158.3 (Cq, rot.1/rot.2, dia.1), 157.7/157.6 (Cq, rot.1/rot.2, dia.2), 157.1/157.0 (Cq, rot.1/rot.2, dia.1), 156.6/156.5 (Cq, rot.1/rot.2, dia.2), 156.2/156.1 (Cq, rot.1/rot.2, dia.1), 156.0/155.7 (Cq, rot.1/rot.2, dia.2), 137.0/136.9 (Cq, rot.1/rot.2), 136.8/136.7 (Cq, rot.1/rot.2), 136.6 (Cq), 129.3 (CH), 129.2 (CH), 129.1 (CH), 129.0 (2 × CH), 128.9 (CH), 128.8 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (CH), 128.0 (CH), 72.0/71.8 (CH, rot.1/rot.2, dia.1), 71.4/70.9 (CH, rot.1/rot.2, dia.2), 69.6/68.6 ($CH_2$, rot.1/rot.2, dia.1), 68.5 ($CH_2$), 68.4/68.3 ($CH_2$, rot.1/rot.2, dia.1), 67.9/67.8 ($CH_2$, rot.1/rot.2, dia.2), 67.7/67.5 ($CH_2$, rot.1/rot.2, dia.2), 67.4/67.2 ($CH_2$, rot.1/rot.2, dia.1), 56.0/55.9 (CH, rot.1/rot.2, dia.2), 55.3/54.9 (CH, rot.1/rot.2, dia.1), 14.3/14.2 ($CH_3$, rot.1/rot.2, dia.1), 13.8/13.7 ($CH_3$, rot.1/rot.2, dia.2); ESI-HRMS calcd for $C_{27}H_{28}N_6O_6Na^+$ $[M + Na]^+$ 555.1963, found 555.1952. Enantiomeric excess is 97/97% determined by SFC (Chiralpak AD-H, $CO_2$/MeOH = 90/10, flow rate = 4.0 mL/min, 210 nm). First diastereomer: minor isomer, $t_R$ = 14.3 min; major isomer, $t_R$ = 22.1 min. Second diastereomer: major isomer, $t_R$ = 14.1 min; minor isomer, $t_R$ = 21.7 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}hex-5-en-3-yl]carbamate (**9e**).* Compound **9e** was obtained from the corresponding *E*-enecarbamate (**1a**, 21.9 mg, 0.1 mmol) as a colorless oil (42.6 mg, dr 1:2) in 84% yield: $[\alpha]^{23}_D$ + 20.4 (*c* 1.0, $CHCl_3$); IR 3311, 2970, 1717, 1521, 1455, 1411, 1307, 1217, 1026, 740, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.50 (br s, 1H, NH), 7.41−7.24 (m, 15H), 7.18 (br s, 1H, NH), 6.03−5.86 (m, 0.2H, rot.1), 5.86−5.66 (m, 0.8H, rot.2), 5.57−5.37 (m, 2H), 5.27−4.84 (m, 7H), 4.36−4.26 (m, 0.5H, rot.1), 4.26−4.12 (m, 0.5H, rot.2), 3.79−3.68 (m, 0.4H, rot.1), 3.68−3.59 (m, 0.4H, rot.2), 3.59−3.47 (m, 0.1H, rot.3), 3.47−3.35 (m, 0.1H, rot.4), 1.27−1.04 (m, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of diastereomers and rotamers: 158.2 (Cq), 157.3/157.0 (Cq, rot.1/rot.2), 156.8/156.5 (Cq, rot.1/rot.2), 137.4 (Cq), 136.3/136.2 (Cq, rot.1/rot.2), 135.4/135.3 (Cq, rot.1/rot.2), 134.9 (CH), 129.5 (2 × CH), 129.4 (2 × CH), 129.2 (2 × CH), 129.1 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.5 (CH), 128.4 (CH), 117.9/117.6 ($CH_2$, rot.1/rot.2), 69.9/68.3 ($CH_2$, rot.1/rot.2), 68.0 ($CH_2$), 67.1/63.9 ($CH_2$, rot.1/rot.2), 57.7/57.5 (CH, rot.1/rot.2, dia.1), 56.9/56.7 (CH, rot.1/rot.2, dia.2), 54.8/54.2 (CH, rot.1/rot.2), 36.9/35.7 ($CH_2$, rot.1/rot.2), 15.4/14.0 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{30}H_{33}N_3O_6Na$ $[M + Na]^+$ 554.2262, found 554.2279. Enantiomeric excess is 98/98% determined by HPLC (Chiralpak AD-H, heptane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, 214 nm). First diastereomer: major isomer, $t_R$ = 17.2 min; minor isomer, $t_R$ = 19.8 min. Second diastereomer: major isomer, $t_R$ = 9.6 min; minor isomer, $t_R$ = 39.0 min.

**General Procedure for the Enantioselective and Diastereoselective Synthesis of Trimethoxybenzene-Substituted Vicinal Diamines.** Under argon, the *E*-enecarbamate (0.1 mmol) was dissolved in $CH_2Cl_2$ (0.4 mL) in a flame-dried flask containing activated powdered 3 Å molecular sieves. The solution was stirred at room temperature for 10 min before being cooled to −45 °C and stirred for an additional 10 min. Dibenzyl azodicarboxylate (44.7 mg, 0.15 mmol, 1.5 equiv) dissolved in $CH_2Cl_2$ (0.3 mL) was added, and the reaction mixture was stirred for 10 min. Then EtSH (7.7 $\mu$L, 0.1 mmol, 1.0 equiv) and finally the (*S*)-phosphoric acid (5.0 mg, 0.01 mmol, 0.1 equiv) in $CH_2Cl_2$ (0.3 mL) were added, and the reaction mixture was stirred at −45 °C for 16 h. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (heptane/EtOAc 6/4).

The obtained product was dissolved in $CH_2Cl_2$ (1.0 mL) and cooled to 0 °C. A solution of 1,3,5-trimethoxybenzene (18.5 mg, 0.11 mmol, 1.1 equiv) in $CH_2Cl_2$ (0.5 mL) was added. Then *N*-iodosuccinimide (6.7 mg, 0.03 mmol, 0.3 equiv) dissolved in $CH_2Cl_2$ (0.5 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h, monitoring the evolution by TLC. The mixture was quenched with a fresh solution of $Na_2S_2O_3$ and allowed to reach room temperature. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (heptane/EtOAc 6/4) to afford the desired product.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-1-(2,4,6-trimethoxyphenyl)propyl]-carbamate (**11a**).* Compound **11a** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (58.5 mg, dr >95:5) in 89% yield: $[\alpha]^{23}_D$ +54.4 (*c* 1.0, $CHCl_3$); IR 3434, 3308, 2942, 1714, 1592, 1497, 1454, 1214, 1204, 1122, 1024, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 7.82−7.70 (m, 1H, NH),7.49−7.15 (m, 15H), 6.63 (br s, NH), 6.22−6.04 (m, 1H), 6.02−5.84 (m, 1H), 5.33−4.96 (m, 6H), 4.96−4.86 (m, 1H), 4.86−4.52 (m, 1H), 3.90−3.72 (m, 7.5H, rot.1), 3.23 (s, 1.5H, rot.2), 0.96 (d, *J* = 6.6 Hz, 2.2H, rot.1), 0.86 (d, *J* = 6.6 Hz, 0.8H, rot.2); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.1/161.0 (Cq, rot.1/rot.2), 159.3/159.1 (Cq, rot.1/rot.2), 158.4 (Cq), 157.3 (Cq), 157.1 (Cq), 156.6 (Cq), 136.4 (Cq), 136.2 (Cq), 136.1 (Cq), 128.7 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 106.8/106.6 (Cq, rot.1/rot.2), 90.8/90.7 (2 × CH, rot.1/rot.2), 68.4/68.0 ($CH_2$, rot.1/rot.2), 67.6/67.5 ($CH_2$, rot.1/rot.2), 67.3/66.9 ($CH_2$, rot.1/rot.2), 56.3 ($CH_3$), 55.9/55.8 ($CH_3$, rot.1/rot.2), 55.4 ($CH_3$), 55.6/55.0 (CH, rot.1/rot.2), 48.7/48.6 (CH, rot.1/rot.2), 14.2/14.0/13.8 ($CH_3$, rot.1/rot.2/rot.3); ESI-HRMS calcd for $C_{36}H_{39}N_3O_9Na^+$ $[M + Na]^+$ 680.2579, found 680.2602. Enantiomeric excess is 99% determined by HPLC (Chiralpak AD-H,


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

heptane/*i*PrOH = 85/15, flow rate =1.0 mL/min, 214 nm): major isomer, $t_R$ = 12.2 min; minor isomer, $t_R$ = 25.9 min.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-1-(2,4,6-trimethoxyphenyl)pentyl]-carbamate (**11b**).* Compound **11b** was obtained from the corresponding *E*-enecarbamate (**1b**, 21.9 mg, 0.1 mmol) as a colorless oil (56.9 mg, dr >95:5) in 83% yield: $[\alpha]^{23}_D$ = +48.2 (*c* 1.0, $CHCl_3$); IR 3434, 3289, 2958, 1715, 1592, 1497, 1454, 1204, 1117, 1027, 735, 696 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 8.01−7.66 (m, 1H, NH), 7.55−7.16 (m, 15H), 6.13−5.85 (m, 2H), 5.34−5.28 (br s, NH), 5.28−4.80 (m, 6H), 4.80−4.46 (m, 1H), 4.86−4.52 (m, 1H), 3.93−3.76 (m, 7.5H, rot.1), 3.27 (s, 1.5H, rot.2), 1.75−1.55 (m, 1H), 1.55−1.39 (m, 1H), 1.39−1.32 (m, 1H), 0.98−0.81 (m, 1H), 0.80−0.66 (m, 2.3H, rot.1), 0.60−0.46 (m, 0.7H, rot.2); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.1/161.0 (Cq, rot.1/rot.2), 159.3/159.1 (Cq, rot.1/rot.2), 158.4 (Cq), 157.4/157.3 (Cq, rot.1/rot.2), 157.0/156.9 (Cq, rot.1/rot.2), 156.5 (Cq), 136.5 (Cq), 136.4 (2 × Cq), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 107.02/107.1 (Cq, rot.1/rot.2), 91.0 ($CH_2$), 90.9/90.8 (CH, rot.1/rot.2), 68.3 ($CH_2$), 67.6/67.4 ($CH_2$, rot.1/rot.2), 67.2/66.9 ($CH_2$, rot.1/rot.2), 60.4/59.9 (CH, rot.1/rot.2), 56.0/55.8 ($CH_3$, rot.1/rot.2), 55.4 ($CH_3$), 55.0 ($CH_3$), 47.8/47.7 (CH, rot.1/rot.2), 29.7/29.6 ($CH_2$, rot.1/rot.2), 19.7/19.6 ($CH_2$, rot.1/rot.2), 13.8/13.6 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{38}H_{43}N_3O_9Na^+$ $[M + Na]^+$ 708.2892, found 708.2889. Enantiomeric excess is 98% determined by HPLC (Chiralpak AD-H, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm): minor isomer, $t_R$ = 7.2 min; major isomer, $t_R$ = 10.9 min.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-3-methyl-1-(2,4,6-trimethoxyphenyl)-butyl]carbamate (**11c**).* Compound **11c** was obtained from the corresponding *E*-enecarbamate (**1c**, 21.9 mg, 0.1 mmol) as a colorless oil (63.8 mg, dr >95:5) in 93% yield: $[\alpha]^{23}_D$ + 49.9 (*c* 1.0, $CHCl_3$); IR 3433, 3288, 2959, 1715, 1609, 1499, 1455, 1215, 1121, 1036, 740, 697 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 8.19−7.96 (m, 1H, NH), 7.50−7.16 (m, 15H), 6.12 (br s, NH), 5.97−5.67 (m, 1H), 5.67−5.50 (m, 1H), 5.33−4.97 (m, 6H), 4.97−4.81 (m, 1H), 4.81−4.61 (m, 1H), 3.93−3.71 (m, 7.9H, rot.1), 3.33 (s, 1.1H, rot.2), 1.59−1.40 (m, 1H), 1.10−1.00 (m, 2.5H, rot.1), 0.84 (d, *J* = 6.9 Hz, 3H, rot.2), 0.75 (d, *J* = 7.2 Hz, 0.5H, rot.3); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.2/161.1 (Cq, rot.1/rot.2), 158.1 (Cq), 157.8 (Cq), 157.2 (Cq), 156.9/156.7 (Cq, rot.1/rot.2), 156.3 (Cq), 136.5 (Cq), 136.4 (2 × Cq), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 107.4 (Cq), 91.0 (2 × $CH_2$), 68.3 ($CH_2$), 68.0/67.8 (CH, rot.1/rot.2), 67.4/67.3 ($CH_2$, rot.1/rot.2), 67.2/67.0 ($CH_2$, rot.1/rot.2), 55.9/55.8 ($CH_3$, rot.1/rot.2), 55.4 ($CH_3$), 55.1 ($CH_3$), 46.5/46.4 (CH, rot.1/rot.2), 29.3/29.2 (CH, rot.1/rot.2), 20.6/20.4/20.3 ($CH_3$, rot.1/rot.2/rot.3), 16.4/16.0 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{38}H_{43}N_3O_9Na$ $[M + Na]^+$ 708.2892, found 708.2909. Enantiomeric excess is 98% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm): major isomer, $t_R$ = 14.4 min; minor isomer, $t_R$ = 16.2 min.

*Benzyl N-[(1S,2S)-6-(Benzyloxy)-2-{[(benzyloxy)carbonyl]-({[(benzyloxy)carbonyl]amino})amino}-1-(2,4,6-trimethoxyphenyl)-hexyl]carbamate (**11d**).* Compound **11d** was obtained from the corresponding *E*-enecarbamate (**1d**, 48.8 mg, 0.1 mmol) as a colorless oil (51.6 mg, dr >95:5) in 64% yield: $[\alpha]^{23}_D$ +23.4 (*c* 1.0, $CHCl_3$); IR 3432, 3296, 2941, 1716, 1610, 1499, 1455, 1215, 1120, 1028, 738, 697 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 7.82−7.63 (m, 1H, NH), 7.39−7.00 (m, 15H), 6.06−5.76 (m, 3H), 5.22−4.66 (m, 7H), 4.64−4.52 (m, 0.5H, rot.1), 4.47−4.33 (m, 0.5H, rot.2), 4.33−4.17 (m, 2H), 3.79−3.61 (m, 8.5H, rot.1), 3.29−3.17 (m, 2H), 3.14 (s, 0.5H, rot.2), 1.69−0.71 (m, 6H + $H_{16}$ + $H_{17}$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.2/161.0 (Cq, rot.1/rot.2), 159.2/159.0 (Cq, rot.1/rot.2), 158.4 (Cq), 157.4/157.3 (Cq, rot.1/rot.2), 157.0/156.9 (Cq, rot.1/rot.2), 156.5 (Cq), 138.9/138.8 (2 × Cq, rot.1/rot.2), 136.4 (Cq), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.8 (2 × CH), 127.7 (2 × CH), 127.5 (2 × CH), 127.4 (2 × CH), 127.2 (2 × CH), 107.1/107.0 (Cq, rot.1/rot.2), 91.1/91.0 (CH, rot.1/rot.2), 90.9 ($CH_2$), 72.9 ($CH_2$), 70.6/70.3 ($CH_2$, rot.1/rot.2), 68.3/68.0 ($CH_2$, rot.1/rot.2), 67.7/67.6 ($CH_2$, rot.1/rot.2), 67.4/66.9 ($CH_2$, rot.1/rot.2), 60.7/60.1 (CH, rot.1/rot.2), 56.0/55.9 ($CH_3$, rot.1/rot.2), 55.4 ($CH_3$), 55.1 ($CH_3$), 47.9/47.7 (CH, rot.1/rot.2), 29.4/29.3 ($CH_2$, rot.1/rot.2), 27.4/27.1 ($CH_2$, rot.1/rot.2), 23.3/23.0 ($CH_2$, rot.1/rot.2); ESI-HRMS calcd for $C_{45}H_{51}N_3O_{10}Na^+$ $[M + Na]^+$ 828.3467, found 828.3487. Enantiomeric excess is 98% determined by HPLC (Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL/min, 214 nm): minor isomer, $t_R$ = 52.4 min; major isomer, $t_R$ = 66.7 min.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-5-[(tert-butyldiphenylsilyl)oxy]-1-(2,4,6-trimethoxyphenyl)pentyl]carbamate (**11e**).* Compound **11e** was obtained from the corresponding *E*-enecarbamate (**1e**, 47.4 mg, 0.1 mmol) as a colorless oil (53.6 mg, dr >95:5) in 57% yield: $[\alpha]^{23}_D$ + 24.3 (*c* 1.0, $CHCl_3$); IR 3433, 3280, 2936, 1715, 1593, 1498, 1455, 1214, 1127, 742, 698 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 7.83−7.65 (m, 1H, NH), 7.49−6.91 (m, 15H), 6.09−5.77 (m, 3H), 5.28−4.58 (m, 8H), 3.76−3.60 (m, 8.5H, rot.1), 3.56−3.32 (m, 2H), 3.10 (s, 0.5H, rot.2), 1.63−1.48 (m, 2H), 1.48−1.01 (m, 2H), 0.84−0.69 (m, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.2/161.1 (Cq, rot.1/rot.2), 159.3/159.0 (Cq, rot.1/rot.2), 158.4 (Cq), 157.5/157.4 (Cq, rot.1/rot.2), 157.2/156.9 (Cq, rot.1/rot.2), 156.5 (Cq), 136.4 (2 × Cq), 135.6 (2 × Cq, rot.1/rot.2), 134.5 (Cq), 134.4 (Cq), 129.6 (2 × CH), 128.7 (3 × CH), 128.6 (2 × CH), 128.4 (3 × CH), 128.2 (3 × CH), 127.9 (2 × CH), 127.7 (3 × CH), 127.5 (2 × CH), 127.4 (3 × CH), 127.3 (2 × CH), 107.2/107.1 (Cq, rot.1/rot.2), 91.3/91.2 (CH, rot.1/rot.2), 91.1 ($CH_2$), 69.7/68.4 ($CH_2$, rot.1/rot.2), 67.8/67.6 ($CH_2$, rot.1/rot.2), 67.3/67.0 ($CH_2$, rot.1/rot.2), 63.6/63.5 ($CH_2$, rot.1/rot.2), 60.8/60.6 (CH, rot.1/rot.2), 56.1 ($CH_3$), 55.9 ($CH_3$), 55.4/55.1 ($CH_3$, rot.1/rot.2), 48.1/47.8 (CH), 29.8/29.7 ($CH_2$), 26.9 (3 × $CH_3$), 24.1/24.0 ($CH_2$), 19.3 (Cq); ESI-HRMS calcd for $C_{54}H_{61}N_3O_{10}SiNa^+$ $[M + Na]^+$ 962.4018, found 962.4029. Enantiomeric excess is 97% determined by HPLC (Chiralpak OD-H, hexane/*i*PrOH = 99/1, flow rate = 1.0 mL/min, 214 nm): major isomer, $t_R$ = 62.8 min; minor isomer, $t_R$ = 74.6 min.

*Benzyl N-[(1S,2S,4R)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-4,8-dimethyl-1-(2,4,6-trimethoxyphenyl)-non-7-en-1-yl]carbamate (**11f**).* Compound **11f** was obtained from the corresponding *E*-enecarbamate (**1f**, 30.1 mg, 0.1 mmol) as a colorless oil (51.4 mg, dr >95:5) in 67% yield: $[\alpha]^{23}_D$ +21.4 (*c* 1.0, $CHCl_3$); IR 3434, 3293, 2937, 1715, 1609, 1498, 1454, 1214, 1204, 1119, 1026, 736, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 7.89−7.86 (m, 1H, NH), 7.49−7.07 (m, 15H), 6.15−6.06 (m, 2H), 5.91−5.81 (br s, NH), 5.36−5.23 (m, 1H), 5.23−4.79 (m, 6H), 5.15−5.00 (m, 1H), 4.79−4.59 (m, 1H), 3.93−3.72 (m, 7.3H, rot.1), 3.27 (s, 1.7H, rot.2), 1.93−1.74 (m, 2H), 1.65 (s, 2.5H, rot.1), 1.60 (s, 0.5H, rot.2), 1.55 (s, 2.5H, rot.1), 1.47 (s, 0.5H, rot.2), 1.63−1.49 (m, 1H), 1.35−1.19 (m, 1H), 1.15−0.89 (m, 2H), 0.73 (d, *J* = 6.6 Hz, 1.5H, rot.1), 0.63 (d, *J* = 6.6 Hz, 1.5H, rot.2), 0.57−0.45 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 161.1/161.0 (Cq, rot.1/rot.2), 159.2/159.0 (Cq, rot.1/rot.2), 158.4 (Cq), 157.3/157.2 (Cq, rot.1/rot.2), 157.0 (Cq), 156.3 (Cq), 136.4 (Cq), 136.3 (2 × Cq), 128.6/128.7 (2 × CH, rot.1/rot.2), 128.5/124.4 (2 × CH, rot.1/rot.2), 128.3/128.2 (2 × CH, rot.1/rot.2), 128.1/128.0 (2 × CH), 127.8 (CH), 127.4 (CH), 127.2/127.1 (2 × CH, rot.1/rot.2), 125.6/125.5 (2 × CH, rot.1/rot.2), 125.4 (Cq), 125.1 (CH), 107.3/107.1 (Cq, rot.1/rot.2), 91.0/90.9 (CH, rot.1/rot.2), 90.8 ($CH_2$), 68.4/68.0 ($CH_2$, rot.1/rot.2), 67.6/67.4 ($CH_2$, rot.1/rot.2), 67.2/66.9 ($CH_2$, rot.1/rot.2), 58.7/58.0 (CH, rot.1/rot.2), 56.0/55.8 ($CH_3$, rot.1/rot.2), 55.4 ($CH_3$), 54.9 ($CH_3$), 48.0/47.8 (CH, rot.1/rot.2), 38.2/38.1 ($CH_2$, rot.1/rot.2), 35.0/34.8 ($CH_2$, rot.1/rot.2), 29.5/29.3 ($CH_2$, rot.1/rot.2), 25.8 ($CH_3$), 25.6/25.4 ($CH_2$, rot.1/rot.2), 18.8/18.7 ($CH_3$, rot.1/rot.2), 17.6 ($CH_3$); ESI-HRMS calcd for $C_{44}H_{53}N_3O_9Na^+$ $[M + Na]^+$ 790.3674, found 790.3642. Enantiomeric excess is 98% determined by HPLC



DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

(Chiralpak IA, heptane/*i*PrOH = 95/5, flow rate = 1.0 mL/min, 214 nm): minor isomer, $t_R$ = 17.2 min; major isomer, $t_R$ = 22.3 min.

**General Procedure for the Enantioselective Synthesis of Heterocycle-Substituted Vicinal Diamines.** Under argon, the *E*-enecarbamate (0.1 mmol) was dissolved in $CH_2Cl_2$ (0.4 mL) in a flame-dried flask containing activated powdered 3 Å molecular sieves. The solution was stirred at room temperature for 10 min before being cooled to −45 °C and stirred for additional 10 min. Dibenzyl azodicarboxylate (44.7 mg, 0.15 mmol, 1.5 equiv) dissolved in $CH_2Cl_2$ (0.3 mL) was added, and the reaction mixture was stirred for 10 min. Then EtSH (7.7 μL, 0.1 mmol, 1.0 equiv) and finally the (*S*)-phosphoric acid (5.0 mg, 0.01 mmol, 0.1 equiv) in $CH_2Cl_2$ (0.3 mL) were added, and the reaction mixture was stirred at −45 °C for 16 h. Solvent was removed under reduced pressure, and the residue was purified over silica gel (heptane/EtOAc 6/4).

The obtained product was dissolved in $CH_2Cl_2$ (0.5 mL) and cooled to 0 °C. A solution of the nucleophile (0.3 mmol, 3.0 equiv) in $CH_2Cl_2$ (1.0 mL) was added. Then *N*-iodosuccinimide (0.05 mmol, 0.5 equiv) dissolved in $CH_2Cl_2$ (0.5 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h, monitoring the evolution by TLC. The mixture was quenched with a fresh solution of $Na_2S_2O_3$ and allowed to reach room temperature. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under vacuum. The residue was purified on silica gel twice (heptane/EtOAc 6/4 followed by $CHCl_3$/EtOAc 7/3) to afford the desired compound.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-(2,4-dimethoxyphenyl)propyl]carbamate (**11g**).* Compound **11g** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (45.8 mg, dr 1:1) in 73% yield: $[\alpha]^{23}_D$ +55.7 (*c* 1.0, $CHCl_3$); IR 3433, 3303, 2936, 1753, 1714, 1613, 1502, 1455, 1407, 1302, 1209, 1027, 754, 697 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ (ppm) mixture of diastereosiomers 1:1 and rotamers: 7.65 (br s, 0.5H, NH), 7.52 (br s, 0.5H, NH), 7.42−7.07 (m, 15H), 7.03−6.88 (m, 1H), 6.41−6.24 (m, 2H), 5.95−5.70 (m, 1H), 5.24−4.69 (m, 6H), 4.65−4.34 (m, 1H), 3.81−3.62 (m, 4.8H, rot.1), 3.24 (s, 1.2H, rot.2), 0.87 (d, *J* = 6.6 Hz, 2.3H, rot.1), 0.75 (d, *J* = 7.5 Hz, 0.7H, rot.2); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ (ppm) mixture of diastereosiomers 1:1 and rotamers: 161.0/160.9 (Cq, rot.1/rot.2), 159.3/159.0 (Cq, rot.1/rot.2), 158.4/157.9 (Cq, rot.1/rot.2), 157.2/157.0 (Cq, rot.1/rot.2), 156.8/156.7 (Cq, rot.1/rot.2), 136.2 (Cq), 131.4/131.1 (Cq, rot.1/rot.2), 130.2/130.0 (Cq, rot.1/rot.2), 129.5/129.4 (CH, rot.1/rot.2), 128.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6/127.4 (CH), 105.4/105.0 (Cq, rot.1/rot.2), 104.4/104.2 (CH, rot.1/rot.2), 99.3/99.0 (CH, rot.1/rot.2), 68.4/68.0 ($CH_2$, rot.1/rot.2), 67.8/67.6 ($CH_2$, rot.1/rot.2), 67.5/66.9 ($CH_2$, rot.1/rot.2), 56.3/56.0 (CH, rot.1/rot.2), 55.6/55.5 ($CH_3$, rot.1/rot.2), 55.4/55.3 ($CH_3$, rot.1/rot.2), 54.9 (CH), 17.0/16.6 ($CH_3$, rot.1/rot.2, dia.1), 15.4/15.1 ($CH_3$, rot.1/rot.2, dia.2); ESI-HRMS calcd for $C_{35}H_{37}N_3O_8Na$ $[M + Na]^+$ 650.2473, found 650.2457. Enantiomeric excess is 99/97% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, 254 nm). Major diastereomer: minor isomer, $t_R$ = 31.0 min; major isomer, $t_R$ = 42.4 min. Minor diastereomer: major isomer, $t_R$ = 34.6 min; minor isomer, $t_R$ = 65.6 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-(1H-pyrazol-1-yl)propyl]carbamate (**11h**).* Compound **11h** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (35.7 mg, dr 1:2) in 64% yield: $[\alpha]^{23}_D$ +6.5 (*c* 1.0, $CHCl_3$); IR 3306, 3033, 1699, 1498, 1402, 1299, 1215, 1041, 1016, 733, 695 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) δ (ppm) mixture of diastereomers and rotamers: 7.66 (d, *J* = 2.0 Hz, 0.2H, rot.1), 7.1 (d, *J* = 2.0 Hz, 0.8H, rot.2), 7.52 (d, *J* = 2.0 Hz, 0.2H, rot.1), 7.43 (d, *J* = 2.0 Hz, 0.8H, rot.2), 7.41−7.13 (m, 15H), 6.64 (br s, 1H, NH), 6.22 (dd, app t, *J* = 2.0 Hz, 0.2H, rot.1), 6.25 (dd, app t, *J* = 2.0 Hz, 0.8H, rot.2), 5.95−5.84 (m, 1H), 5.22−4.88 (m, 6H), 4.80−4.71 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 2.4H, rot.1), 0.94 (d, *J* = 6.5 Hz, 0.6H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$) δ (ppm) mixture of diastereomers and rotamers: 158.6 (Cq), 157.5 (Cq), 156.6 (Cq), 150.9 (Cq), 141.2 (Cq), 140.4 (2 × Cq), 137.4 (Cq), 129.6 (2 × CH), 129.5 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 106.5/106.2 (CH, rot.1/rot.2), 70.8 (CH), 68.9/68.5 ($CH_2$, rot.1/rot.2), 68.2 ($CH_2$), 67.7/67.5 ($CH_2$, rot.1/rot.2), 58.2/56.8 (CH, rot.1/rot.2), 15.0/14.5 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{30}H_{31}N_5O_6Na$ $[M + Na]^+$ 580.2167, found 580.2168. Enantiomeric excess is 99/89% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: minor isomer, $t_R$ = 31.2 min; major isomer, $t_R$ = 78.3 min. Minor diastereomer: major isomer, $t_R$ = 36.4 min; minor isomer, $t_R$ = 64.0 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-(2H-indazol-2-yl)propyl]carbamate (**11i**).* Compound **11i** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (44.4 mg, dr 1:2) in 73% yield: $[\alpha]^{23}_D$ +32.9 (*c* 1.0, $CHCl_3$); IR 3294, 3033, 1700, 1514, 1408, 1293, 1229, 1214, 1118, 1025, 909, 729, 695 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) δ (ppm) mixture of diastereomers and rotamers: 8.24 (s, 1H), 7.69 (dd, *J* = 1.0 Hz and *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 7.0 Hz, 1H), 7.54 (br s, 1H, NH), 7.45−7.25 (m, 16H), 7.80 (t, *J* = 7.0 Hz, 1H), 6.92 (br s, 1H, NH), 6.15 (d, app t, *J* = 8.5 Hz, 1H), 5.24−4.99 (m, 6H), 4.93−4.85 (m, 1H), 1.31 (s, 0.4H, rot.1), 0.97 (d, *J* = 6.5 Hz, 2.6H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$) δ (ppm) mixture of diastereomers and rotamers: 158.0 (Cq), 156.8 (Cq), 156.6 (Cq), 150.0/149.5 (Cq), 137.5 (Cq), 137.2 (Cq), 136.9 (Cq), 129.4 (2 × CH), 129.3 (2 × CH), 129.2 (2 × CH), 129.1 (CH), 129.0 (2 × CH), 128.9 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 127.3 (CH), 125.2 (Cq), 122.7 (CH), 122.1 (CH), 121.8 (CH), 121.5 (CH), 72.3 (CH), 68.8 ($CH_2$), 68.4/68.2 ($CH_2$, rot.1/rot.2), 67.5/67.6 ($CH_2$, rot.1/rot.2), 58.4/57.3 (CH, rot.1/rot.2), 15.1/14.5/13.9 ($CH_3$, rot.1/rot.2/rot.3); ESI-HRMS calcd for $C_{34}H_{33}N_5O_6Na$ $[M + Na]^+$ 630.2323, found 630.2334. Enantiomeric excess is >99/95% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: major isomer, $t_R$ = 54.8 min; minor isomer, $t_R$ = 113.4 min. Minor diastereomer: minor isomer, $t_R$ = 31.0 min; major isomer, $t_R$ = 71.2 min.

*Benzyl N-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-(furan-2-yl)propyl]carbamate (**11j**).* Compound **11j** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (40.1 mg, dr 1:2) in 72% yield: $[\alpha]^{23}_D$ = +59.8 (*c* 1.0, $CHCl_3$); IR 3314, 2970, 1738, 1366, 1228, 1217, 1027, 741, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) δ (ppm) mixture of diastereomers and rotamers: 7.43 (s, 1H), 7.39−7.26 (m, 15H), 6.39−6.36 (m, 1H), 6.34 (d, *J* = 3.0 Hz, 1H), 5.99 (br s, 1H, NH), 5.19−4.98 (m, 6H), 4.76 (d, app t, *J* = 9.5 Hz, 1H), 4.61−4.53 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) δ (ppm) mixture of diastereomers and rotamers: 157.3 (Cq), 156.9 (Cq), 156.8 (Cq), 155.3 (Cq), 143.6 ($CH_3$), 137.5 (2 × Cq), 137.4 (Cq), 129.6 (2 × CH), 129.5 (2 × CH), 129.3 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.9 (CH), 128.8 (2 × CH), 128.6 (2 × CH), 111.4 ($CH_2$), 109.3 (CH), 68.8/68.5 ($CH_2$, rot.1/rot.2), 68.0 ($CH_2$), 67.4 ($CH_2$), 56.9/56.4 (CH, rot.1/rot.2), 52.7/52.6 (CH, rot.1/rot.2), 15.3/15.5 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{31}H_{31}N_3O_7Na$ $[M + Na]^+$ 580.2054, found 580.2059. Enantiomeric excess is 98/92% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: minor isomer, $t_R$ = 27.2 min; major isomer, $t_R$ = 59.1 min. Minor diastereomer: major isomer, $t_R$ = 22.4 min; minor isomer, $t_R$ = 32.9 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(1H-indol-3-yl)propan-2-yl](benzyloxy)carbohydrazide (**12a**).* Compound **12a** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (45.2 mg) in 79% yield: $[\alpha]^{23}_D$ = −32.5 (*c* 1.0, $CHCl_3$); IR 3340, 2981, 1693, 1497, 1455, 1405, 1335, 1215, 1052, 737, 695 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) δ (ppm) mixture of rotamers: 8.98 (br s, NH), 8.88 (br s, NH), 7.63 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.36−7.29 (m, 14H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 7.00 (t, *J* = 7.0 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.62 (br s, NH), 5.33−5.21 (m, 1H), 5.16−4.94 (m, 4H), 4.75 (d, *J* = 10.5 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 0.6H, rot.1), 1.22 (d, *J* = 6.5


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

Hz, 2.4H, rot.2); $^{13}$C NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of rotamers: 157.9/157.8 (Cq, rot.1/rot.2), 156.7/156.6 (Cq, rot.1/rot.2), 137.6 (2 × Cq), 137.5 (2 × Cq), 137.7 (2 × Cq), 129.6 (2 × CH), 129.5 (CH), 129.4 (CH), 129.3 (2 × CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 124.0 (CH), 123.7 (CH), 122.8 (CH), 122.5 (CH), 122.4 (CH), 122.3 (CH), 119.9/119.8 (CH, rot.1/rot.2), 119.5 (CH), 117.5 (2 × Cq), 112.4 (CH), 112.2 (CH), 67.1/67.8 ($CH_2$, rot.1/rot.2), 67.0 ($CH_2$), 58.5/56.8 (CH, rot.1/rot.2), 38.8/38.4 (CH, rot.1/rot.2), 17.8/17.3 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{35}H_{32}N_4O_4Na$ $[M + Na]^+$ 595.2316, found 595.2325. Enantiomeric excess is >99% determined by HPLC (Chiralpak AD-H, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 41.3 min; major isomer, $t_R$ = 104.8 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(5-bromo-1H-indol-3-yl)propan-2-yl](benzyloxy)carbohydrazide (**12b**).* **12b** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (70.9 mg) in 97% yield. $[\alpha]^{23}_D$ −29.4 (*c* 1.0, $CHCl_3$); IR 3346, 2970, 1699, 1588, 1455, 1405, 1337, 1215, 1054, 730, 696 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.08 (br s, NH), 8.96 (br s, NH), 7.67 (s, 1H), 7.62 (s, 1H), 7.34−7.12 (m, 14H), 7.11 (dd, *J* = 1.5 and *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 1.5 Hz and *J* = 8.5 Hz, 1H), 6.81 (br s, 0.3H, rot.1, NH), 6.72 (br s, 0.7H, rot.2, NH), 5.26−5.17 (m, 1H), 5.17−4.91 (m, 4H), 4.84−4.76 (m, 0.2H, rot.1), 4.66 (d, *J* = 10.5 Hz, 0.8H, rot.2), 1.29 (d, *J* = 7.0 Hz, 0.6H, rot.1), 1.20 (d, *J* = 6.0 Hz, 2.4H, rot.2); $^{13}$C NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of rotamers: 157.8/157.2 (Cq, rot.1/rot.2), 156.6 (Cq), 138.3 (Cq), 137.6/137.5 (Cq, rot.1/rot.2), 136.2 (Cq), 136.1 (Cq), 129.7 (CH), 129.4 (CH), 129.0 (2 × CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (2 × CH), 128.2 (CH), 125.7 (2 × Cq), 125.0 (2 × CH), 124.8/124.2 (2 × Cq, rot.1/rot.2), 122.4/122.1 (2 × CH, rot.1/rot.2), 117.3 (2 × Cq), 114.3/114.0 (2 × CH, rot.1/rot.2), 112.7/112.4 (2 × CH, rot.1/rot.2), 68.6/67.8 ($CH_2$, rot.1/rot.2), 67.0/66.8 ($CH_2$, rot.1/rot.2), 58.1/58.8 (CH, rot.1/rot.2), 38.6/38.2 (CH, rot.1/rot.2), 17.9/17.3 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{35}H_{30}Br_2N_4O_4Na$ $[M + Na]^+$ 751.0526, found 751.0515. Enantiomeric excess is 98% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm): major isomer, $t_R$ = 24.9 min; minor isomer, $t_R$ = 31.1 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(5-nitro-1H-indol-3-yl)-propan-2-yl](benzyloxy)carbohydrazide (**12c**).* Compound **12c** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a yellow oil (57.6 mg) in 87% yield: $[\alpha]^{23}_D$−47.8 (*c* 1.0, $CHCl_3$); IR 3319, 2955, 1697, 1517, 1471, 1455, 1329, 1217, 737, 696 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.61 (br s, 0.8 H, rot.1, NH), 9.54 (br s, 0.4H, rot.2, NH), 9.49 (br s, 0.8H, rot.3, NH), 8.70 (s, 0.4H, rot.2), 8.61 (d, *J* = 2.5 Hz, 0.8H, rot.1), 8.52 (s, 0.8H, rot.3), 8.03 (dd, *J* = 2.5 Hz and *J* = 9.5 Hz, 0.4H, rot.2), 7.98 (dd, *J* = 2.5 Hz and *J* = 9.5 Hz, 0.8H, rot.1), 7.93 (dd, *J* = 1.5 Hz and *J* = 8.5 Hz, 0.8H, rot.3), 7.59 (s, 0.8H, rot.1), 7.53 (d, *J* = 2.0 Hz, 1.2H, rot.2 + rot.3), 7.50 (d, *J* = 9.0 Hz, 0.4H, rot.2), 7.47 (d, *J* = 9.5 Hz, 0.8H, rot.1), 7.53 (d, *J* = 9.0 Hz, 0.8H, rot.3), 7.40−7.16 (m, 10H), 6.98 (br s, 1H, NH), 5.31 (m, 0.6H, rot.1 + rot.2), 5.25 (dq, app t, *J* = 8.5 Hz, 0.4H, rot.3), 5.15−4.93 (m, 4H), 4.89 (d, *J* = 10.5 Hz, 0.6H, rot.1 + rot.2), 4.85 (d, *J* = 8.5 Hz, 0.4H, rot.3), 1.32 (d, *J* = 7.0 Hz, 1.2H, rot.1 + rot.2), 1.24 (d, *J* = 6.5 Hz, 1.8H, rot.2 + rot.3); $^{13}$C NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of rotamers: 159.1 (Cq), 158.6/157.1 (Cq, rot.1/rot.2), 143.0/142.8 (2 × Cq, rot.1/rot.2), 142.6 (2 × Cq), 141.2/141.1 (2 × Cq, rot.1/rot.2), 138.1 (Cq), 137.7 (Cq), 130.1 (2 × CH), 129.7 (2 × CH), 129.5 (CH), 129.4 (2 × CH), 129.2/129.3 (CH, rot.1/rot.2), 128.9/128.8 (CH, rot.1/rot.2), 128.5 (CH), 127.0 (2 × CH), 118.9 (2 × Cq), 118.6/118.4 (2 × CH, rot.1/rot.2), 118.0/118.8 (2 × CH, rot.1/rot.2), 113.4/113.1 (2 × CH, rot.1/rot.2), 68.9/68.8 ($CH_2$, rot.1/rot.2), 68.6/68.5 ($CH_2$, rot.1/rot.2), 58.5/57.1 (CH, rot.1/rot.2), 38.8 (CH), 18.5/17.9 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{35}H_{30}N_6O_8Na$ $[M + Na]^+$ 685.2017, found 685.2021. Enantiomeric excess is 99% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 31.1 min; major isomer, $t_R$ = 40.5 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(5-cyano-1H-indol-3-yl)-propan-2-yl](benzyloxy)carbohydrazide (**12d**).* Compound **12d** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (43.6 mg) in 70% yield: $[\alpha]^{23}_D$ −24.0 (*c* 1.0, $CHCl_3$); IR 3311, 3016, 2220, 1699, 1409, 1317, 1217, 807, 751, 696 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.49 (br s, 1H, NH), 9.37 (br s, 1H, NH), 8.01 (s, 1H), 7.94 (s, 1H), 7.58−7.41 (m, 6H), 7.40−7.27 (m, 10H), 6.92 (br s, 1H, NH), 5.32−5.21 (m, 1H), 5.15−5.03 (m, 2.6H, rot.1), 5.03−4.90 (m, 1.4H, rot.2), 4.74 (d, *J* = 11.0 Hz, 1H), 1.19 (d, *J* = 6,5 Hz, 3H); $^{13}$C NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 158.0/157.9 (Cq, rot.1/rot.2), 156.2/156.1 (Cq, rot.1/rot.2), 138.8/138.7 (Cq, rot.1/rot.2), 138.6/138.5 (Cq, rot.1/rot.2), 137.1/137.2 (Cq, rot.1/rot.2), 137.0/136.9 (Cq, rot.1/rot.2), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.8/127.6/127.3 (2 × CH, rot.1/rot.2/rot.3), 126.6/126.5 (2 × Cq, rot.1/rot.2), 125.5/125.3/125.1 (2 × CH, rot.1/rot.2/rot.3), 124.9/124.8/124.7 (2 × CH, rot.1/rot.2/rot.3), 121.5/121.4 (2 × Cq, rot.1/rot.2), 117.4/117.3/116.9 (2 × Cq, rot.1/rot.2/rot.3), 113.4/113.0 (2 × CH, rot.1/rot.2), 102.0/101.9 (Cq, rot.1/rot.2), 101.7/101.5 (Cq, rot.1/rot.2), 68.2/67.7 ($CH_2$, rot.1/rot.2), 67.9/67.6 ($CH_2$, rot.1/rot.2), 56.8/55.6/55.3 (CH, rot.1/rot.2/rot.3), 37.9/37.7 (CH, rot.1/rot.2), 17.7/17.6 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{37}H_{31}N_6O_4$ $[M + H]^+$ 623.2401, found 623.2419. Enantiomeric excess is >99% determined by HPLC (Chiralpak IA, heptane/ *i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): major isomer, $t_R$ = 20.5 min; minor isomer, $t_R$ = 31.1 min.

*Methyl 3-[(2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}-1-[5-(methoxycarbonyl)-1H-indol-3-yl]propyl]-1H-indole-5-carboxylate (**12e**).* Compound **12e** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (36.5 mg) in 53% yield: $[\alpha]^{23}_D$ −33.7 ( *c* 1.0, $CHCl_3$); IR 3327, 2950, 1696, 1617, 1436, 1316, 1244, 1110, 751, 697 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.33 (br s, 1H, NH), 9.21 (br s, 1H, NH), 8.41 (s, 1H), 8.32 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.49−7.15 (m, 14H), 6.86 (br s, 1H, NH), 5.26 (m, 1H), 5.16−4.91 (m, 4H), 4.83 (d, *J* = 10.5 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 168.3 (2 × Cq), 157.8 (Cq), 156.4 (Cq), 139.7/139.6 (2 × Cq, rot.1/rot.2), 137.2/137.0 (Cq, rot.1/rot.2), 137.1/136.9 (Cq, rot.1/rot.2), 129.3 (CH), 129.2 (CH), 129.1129.0 (CH, rot.1/rot.2), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.8/127.5 (2 × CH, rot.1/rot.2), 126.5/125.7 (2 × Cq, rot.1/rot.2), 124.1/123.5 (CH, rot.1/rot.2), 123.2/123.0 (CH, rot.1/rot.2), 122.4 (CH), 122.1 (CH), 121.3 (Cq), 120.9 (Cq), 118.1 (2 × Cq), 112.2 (CH, rot.1/rot.2), 111.9/111.8 (CH, rot.1/rot.2), 68.3/67.7 ($CH_2$, rot.1/rot.2), 67.5 ($CH_2$), 55.8/55.3 (CH, rot.1/rot.2), 52.3 ($CH_3$), 52.1 ($CH_3$), 38.0/37.7 (CH, rot.1/rot.2), 17.7/17.2 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{35}H_{32}N_4O_4Na$ $[M + Na]^+$ 595.2316, found 595.2325. Enantiomeric excess is 97% determined by SFC (Chiralpak OD-H, $CO_2$/MeOH = 75/25, flow rate = 4.0 mL/min, 210 nm): minor isomer, $t_R$ = 2.1 min; major isomer, $t_R$ = 4.4 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(3-methyl-1H-indol-2-yl)propan-2-yl](benzyloxy)carbohydrazide (**12f**).* Compound **12f** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (43.4 mg) in 63% yield: $[\alpha]^{23}_D$ −0.2 (*c* 1.0, $CHCl_3$); IR 3390, 2921, 1692, 1458, 1417, 1308, 1215, 741, 697 cm$^{-1}$; $^1$H NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.13 (br s, 1H, NH), 8.93 (br s, 1H, NH), 7.50−6.96 (m, 18H), 5.32−4.88 (m, 5H), 4.81 (d, *J* = 11.0 Hz, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of rotamers: 158.1 (Cq), 157.1 (Cq), 136.9 (Cq), 136.6 (Cq), 136.4 (Cq), 136.2/136.1 (Cq, rot.1/rot.2), 133.6 (Cq), 133.4 (Cq), 129.4/129.3 (CH, rot.1/rot.2), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7/128.6 (CH, rot.1/rot.2), 128.5 (CH), 128.4/128.3 (CH, rot.1/rot.2), 128.0/127.9 (Cq, rot.1/rot.2), 127.7 (CH), 122.1 (CH), 122.0/121.9 (CH, rot.1/rot.2), 119.5/119.4 (2 × CH, rot.1/rot.2), 118.9 (CH), 118.8/118.7 (CH, rot.1/rot.2), 111.6/111.4 (CH, rot.1/rot.2), 111.3/111.2 (CH, rot.1/rot.2), 108.8 (Cq),


DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

108.0 (Cq), 68.1/68.0 ($CH_2$, rot.1/rot.2), 67.8/67.7 ($CH_2$, rot.1/rot.2), 55.2 (CH), 38.7 (CH), 17.4/16.9 ($CH_3$, rot.1/rot.2), 16.5 ($CH_3$), 8.8 ($CH_3$); ESI-HRMS calcd for $C_{37}H_{37}N_4O_4$ $[M + H]^+$ 601.2809, found 601.2800. Enantiomeric excess is 97% determined by HPLC (Chiralpak OD-H, Hexane/*i*PrOH = 98/2, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 24.6 min; major isomer, $t_R$ = 30.2 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(5-methoxy-1H-indol-3-yl)propan-2-yl](benzyloxy)carbohydrazide (**12g**).* Compound **12g** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (13.3 mg) in 21% yield: $[\alpha]^{23}_D$ −26.2 (*c* 0.5, $CHCl_3$); IR 3356, 2937, 1704, 1484, 1455, 1211, 1044, 753, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 8.89 (br s, 1H, NH), 8.78 (br s, 1H, NH), 7.51−7.01 (m, 16H), 6.76 (dt, *J* = 9.5 Hz and *J* = 2.5 Hz, 2H), 6.68 (br s, 1H, NH), 5.26 (m, 1H), 5.10−4.93 (m, 4H), 4.65 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 157.7 (Cq), 156.3 (Cq), 153.8/153.7 (Cq, rot.1/rot.2), 153.6/153.5 (Cq, rot.1/rot.2), 137.3 (Cq), 137.0/136.9 (Cq, rot.1/rot.2), 132.0 (Cq), 131.8/131.9 (Cq, rot.1/rot.2), 129.3 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 124.2 (Cq), 124.0 (Cq), 122.9 (CH), 122.6 (CH), 116.7 (Cq), 116.6/116.5 (Cq, rot.1/rot.2), 112.8 (CH), 112.6/112.5 (CH, rot.1/rot.2), 111.8/111.7 (CH, rot.1/rot.2), 111.5/111.4 (CH, rot.1/rot.2), 101.1 (CH), 100.7/100.5 (CH, rot.1/rot.2), 68.3/67.6 ($CH_2$, rot.1/rot.2), 67.5/67.4 ($CH_2$, rot.1/rot.2), 55.5/55.4 (2 × $CH_3$, rot.1/rot.2), 55.7/55.3 (CH, rot.1/rot.2), 38.4/38.0 (CH, rot.1/rot.2), 17.6/17.2 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{37}H_{36}N_4O_6Na$ $[M + Na]^+$ 655.2527, found 655.2520. Enantiomeric excess is 99% determined by HPLC (Chiralpak IA, heptane/ *i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): major isomer, $t_R$ = 65.9 min; minor isomer, $t_R$ = 73.0 min.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-1-(5-methoxy-1H-indol-3-yl)propyl]-carbamate (**11k**).* Compound **11k** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (21.7 mg, dr >95:5) in 34% yield: $[\alpha]^{23}_D$ + 58.0 (*c* 0.5, $CHCl_3$); IR 3326, 2941, 1709, 1486, 1455, 1299, 1216, 1027, 753, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.18 (br s, 0.1H, rot.1, NH), 9.08 (br s, 0.7H, rot.2, NH), 8.94 (br s, 0.2H, rot.3, NH), 7.75−7.22 (m, 16H), 7.21−7.15 (m, 0.5H), 7.15−7.03 (m, 1H), 7.03−6.90 (m, 0.5H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.89 (br s, 1H, NH), 5.30−4.96 (m, 6H), 4.92 (d, app t, *J* = 9.5 Hz, 1H), 4.87−4.74 (m, 1H), 3.96−3.70 (m, 3H), 1.29 (d, *J* = 7.0 Hz, 0.6H, rot.3), 1.08 (d, *J* = 6.5 Hz, 2.1H, rot.2), 0.89 (d, *J* = 6.5 Hz, 0.3H, rot.1); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 158.0/157.9 (Cq, rot.1/rot.2), 157.6/157.2 (Cq, rot.1/rot.2), 156.9/156.8 (Cq, rot.1/rot.2), 154.4/154.3 (Cq, rot.1/rot.2), 137.8/137.7 (Cq, rot.1/rot.2), 137.4/137.0 (Cq, rot.1/rot.2), 136.9/136.8 (Cq, rot.1/rot.2), 131.8/131.6 (Cq, rot.1/rot.2), 129.3 (CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (2 × CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.9/126.5 (Cq, rot.1/rot.2), 124.9/124.7 (CH, rot.1/rot.2), 113.3/113.2 (CH, rot.1/rot.2), 112.9/112.8 (CH, rot.1/rot.2), 112.6/112.4 (Cq, rot.1/rot.2), 100.1 (CH), 68.6/68.1 ($CH_2$, rot.1/rot.2), 67.6/66.9 ($CH_2$, rot.1/rot.2), 66.8/66.5 ($CH_2$, rot.1/rot.2), 55.5 ($CH_3$), 55.3/55.2 (CH, rot.1/rot.2), 51.0 (CH), 15.7/15.2 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{36}H_{36}N_4O_7Na$ $[M + Na]^+$ 659.2476, found 659.2462. Enantiomeric excess is 99% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 44.9 min; major isomer, $t_R$ = 52.1 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(2-methyl-1H-indol-3-yl)propan-2-yl](benzyloxy)carbohydrazide (**12h**).* Compound **12h** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (22.2 mg) in 37% yield: $[\alpha]^{23}_D$ + 36.4 (*c* 0.5, $CHCl_3$); IR 3355, 2970, 1710, 1459, 1217, 1057, 741, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 8.82 (br s, 1H, NH), 8.77 (br s, 1H, NH), 7.74 (d, *J* = 4.5 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.45−7.16 (m, 12H), 7.03−6.96 (m, 2H), 6.96−6.89 (m, 2H), 6.50 (br s, 1H, NH), 5.68−5.45 (m, 1H), 5.22−4.82 (m, 6H), 4.63 (d, *J* = 9.5 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 1.35 (d, *J* = 6.5 Hz, 0.5H, rot.1), 1.24 (d, *J* = 6.0 Hz, 2.5H, rot.2); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 157.9/157.8 (Cq, rot.1/rot.2), 156.3/156.2 (Cq, rot.1/rot.2), 137.2/137.1 (Cq, rot.1/rot.2), 137.0/136.6 (Cq, rot.1/rot.2), 136.0/135.9 (Cq, rot.1/rot.2), 135.8 (Cq), 133.4 (2 × Cq), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 129.1 (CH), 127.9 (CH), 121.0/120.9 (2 × CH, rot.1/rot.2), 120.6/120.5 (2 × CH, rot.1/rot.2), 119.6/119.5 (2 × Cq, rot.1/rot.2), 119.4/119.2 (2 × CH, rot.1/rot.2), 112.6/112.4 (2 × Cq, rot.1/rot.2), 111.2/111.1 (2 × CH, rot.1/rot.2), 68.2/67.9 ($CH_2$, rot.1/rot.2), 67.6/67.4 ($CH_2$, rot.1/rot.2), 56.1/55.3 (CH, rot.1/rot.2), 38.7/38.4 (CH, rot.1/rot.2), 18.6/18.1 ($CH_3$, rot.1/rot.2), 12.7 ($CH_3$) 12.5/12.2 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{37}H_{36}N_4O_4Na$ $[M + Na]^+$ 623.2629, found 623.2650. Enantiomeric excess is 97% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 49.7 min; major isomer, $t_R$ = 114.4 min.

*Benzyl N-[(1S,2S)-2-{[(Benzyloxy)carbonyl]({[(benzyloxy)-carbonyl]amino})amino}-1-(2-methyl-1H-indol-3-yl)propyl]-carbamate (**11l**).* Compound **11l** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (30.4 mg, dr >95:5) in 49% yield: $[\alpha]^{23}_D$ + 104.8 (*c* 0.5, $CHCl_3$); IR 3333, 3033, 1715, 1501, 1456, 1306, 1218, 1055, 742, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 9.02 (br s, 1H, NH), 7.94−7.16 (m, 17H), 7.14−6.76 (m, 2H), 6.11−5.54 (m, 1H), 5.33−4.72 (m, 7H), 2.38 (s, 3H), 0.95 (d, *J* = 5.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 158.0 (Cq), 157.2 (Cq), 157.0 (Cq), 137.4/137.3 (Cq), 136.9 (Cq), 136.5 (Cq), 136.2/136.1 (Cq), 134.5/134.4 (Cq), 129.4 (CH), 129.3 (CH), 129.2 (2 × CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 121.6 (Cq), 119.8/119.7 (2 × CH, rot.1/rot.2), 119.1 (CH), 111.6/111.5 (CH, rot.1/rot.2), 108.4/108.0 (Cq, rot.1/rot.2), 69.0/68.2 ($CH_2$, rot.1/rot.2), 67.9/67.7 ($CH_2$, rot.1/rot.2), 67.0/66.8 ($CH_2$, rot.1/rot.2), 56.9/55.9 (CH, rot.1/rot.2), 51.6/51.4 (CH, rot.1/rot.2), 15.0/14.8 ($CH_3$, rot.1/rot.2), 11.9/11.5 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{36}H_{36}N_4O_6Na$ $[M + Na]^+$ 643.2527, found 643.2547. Enantiomeric excess is 98% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm): major isomer, $t_R$ = 16.5 min; minor isomer, $t_R$ = 64.5 min.

*N′-[(Benzyloxy)carbonyl]-N′-[(2S)-1,1-bis(5-methoxythiophene-2-yl)propan-2-yl](benzyloxy)carbohydrazide (**12i**).* Compound **12i** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (43.1 mg) in 76% yield: $[\alpha]^{23}_D$ = +2.3 (*c* 1.0, $CHCl_3$); IR 3299, 2942, 1713, 1501, 1406, 1307, 1205, 1028, 753, 697 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3CN$, 70 °C) $\delta$ (ppm) mixture of rotamers: 7.42−7.23 (m, 10H), 6.81 (br s, 1H, NH), 6.59−6.52 (m, 2H), 6.08−6.04 (m, 1H), 6.02−5.96 (m, 1H), 5.19−4.99 (m, 4H), 4.70−4.61 (m, 1H), 4.29 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 2.7H, rot.1), 3.80 (s, 2.9H, rot.2), 3.70−3.65 (m, 0.4H, rot.3), 1.19 (d, *J* = 5.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of rotamers: 166.4 (Cq), 166.0 (Cq), 157.8/157.9 (Cq, rot.1/rot.2), 156.3 (Cq), 137.4 (2 × Cq), 132.4 (2 × Cq), 129.5 (2 × CH), 129.4 (2 × CH), 129.1 (2 × CH), 128.8 (CH), 128.7 (2 × CH), 128.3 (CH), 123.8 (CH), 123.5/123.1 (CH, rot.1/rot.2), 103.7 (2 × $CH_2$), 68.1/68.0 ($CH_2$, rot.1/rot.2), 69.9/68.8 ($CH_2$, rot.1/rot.2), 60.9/60.8 (2 × $CH_3$, rot.1/rot.2), 60.3/59.1 (CH, rot.1/rot.2), 47.5/47.3 (CH, rot.1/rot.2), 17.4/16.9 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{29}H_{30}N_2O_6S_2Na$ $[M + Na]^+$ 589.1437, found 589.1464. Enantiomeric excess is 99% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm): major isomer, $t_R$ = 15.2 min; minor isomer, $t_R$ = 22.8 min.

**General Procedure for the Cleavage of the Hydrazine Bond.** The 1,2-diamine (0.1 mmol, 1.0 equiv) was dissolved in MeOH/AcOH (9/1) (1.0 mL) in a flask under argon. A small scoop of Raney Nickel (excess) was added, and the atmosphere of the flask was purged



DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

under vacuum and flushed with hydrogen. The solution was hydrogenated in a Parr shaker (40−45 psi) for 2 days. Then the suspension was filtered through a bed of Celite and washed with MeOH. The crude was concentrated to afford a slightly green solid which was dissolved in pyridine (1.0 mL) under argon. $Bz_2O$ (or $Ac_2O$) (0.5 mmol, 5.0 equiv) was added, and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with water, the aqueous layer was extracted with EtOAc (3 times), and the combined organic layers were washed with aqueous HCl (1 N) solution, water, saturated $NaHCO_3$ aqueous solution, and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (heptane/EtOAc 6/4) to afford the desired compound.

*Benzyl N-[(1S,2S)-2-(Phenylformamido)-1-(2,4,6-trimethoxyphenyl)propyl]carbamate (**13a**).* Compound **13a** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (33.5 mg, dr >95:5) in 70% yield: $[\alpha]^{23}_D$ + 38.0 (*c* 0.5, $CHCl_3$); IR 3310, 2942, 1716, 1593, 1498, 1455, 1217, 1124, 1027, 755, 697 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of rotamers: 7.83 (dd, *J* = 6.9 Hz and *J* = 1.5 Hz, 2H), 7.51−7.34 (m, 3H), 7.22−7.14 (m, 5H), 6.93 (br s, 1H, NH), 6.23 (br s, 1H, NH), 6.14 (s, 2H), 5.40 (d, app t, *J* = 10.2 Hz, 1H), 4.99 (s, app q, *J* = 7.8 Hz, 2H), 4.72−4.56 (m, 1H), 3.85 (s, 5.3H, rot.1), 3.82 (s, 3.7H, rot.2), 1.03 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) 167.3 (Cq), 161.2 (3 × Cq), 157.9 (Cq), 136.6 (Cq), 134.8 (Cq), 131.3 (CH), 128.6 (2 × CH), 128.2 (4 × CH), 127.2 (3 × CH), 107.3 (Cq), 91.0 (2 × CH, rot.1/rot.2), 66.9 ($CH_2$), 56.0 (CH), 55.5 ($CH_3$), 50.9 (2 × $CH_3$), 50.8 (CH), 18.3 ($CH_3$); ESI-HRMS calcd for $C_{27}H_{30}N_2O_6Na$ $[M + Na]^+$ 501,1996, found 501,2009. Enantiomeric excess is 99% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 254 nm): major isomer, $t_R$ = 7.3 min; minor isomer, $t_R$ = 11.3 min.

*Benzyl N-[(1S,2S)-2-Acetamido-3-methyl-1-(2,4,6-trimethoxyphenyl)butyl]carbamate (**13b**).* Compound **13b** was obtained from the corresponding *E*-enecarbamate (**1c**, 21.9 mg, 0.1 mmol) as a colorless oil (10.7 mg, dr >95:5) in 24% yield: $[\alpha]^{23}_D$ = +44.7 (*c* 0.2, $CHCl_3$); IR 3329, 2954, 1716, 1591, 1486, 1454, 1217, 1126, 1028, 754, 696 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 7.37−7.26 (m, 5H), 6.10 (s, app t, *J* = 10.2 Hz, 2H), 5.23 (d, app t, *J* = 9.6 Hz, 1H), 5.04 (d, AB syst, *J* = 12.6 Hz, 1H), 4.93 (d, AB syst, *J* = 12.6 Hz, 1H), 4.27 (dd, app dt, *J* = 3.6 and 9.6 Hz, 1H), 3.87 (s, app d, *J* = 9.0 Hz, 1.3H, rot.1), 3.80 (s, 4H, rot.2), 3.78 (s, 3.7H, rot.3), 1.78 (s, 3H), 1.46−1.37 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 171.2 (Cq), 161.3 (Cq), 160.0 (2 × Cq), 156.8 (Cq), 138.1 (Cq), 129.1 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 108.1 (Cq), 91.4 (CH), 90.9 (CH), 66.4 ($CH_2$), 57.3 (CH), 56.2/56.1 (2 × $CH_3$, rot.1/rot.2), 55.6 ($CH_3$), 49.4 (CH), 29.4 (CH), 22.8/20.8 ($CH_3$, rot.1/rot.2), 16.1 (2 × $CH_3$); ESI-HRMS calcd for $C_{24}H_{33}N_2O_6$ $[M + H]^+$ 445.2333, found 445.2346. Enantiomeric excess is 98% determined by HPLC (Chiralpak OD-H, hexane/EtOH = 95/5, flow rate = 1.0 mL/min, 214 nm): minor isomer, $t_R$ = 6.4 min; major isomer, $t_R$ = 6.9 min.

*N-[(2S)-1,1-Bis(1H-indol-3-yl)propan-2-yl]benzamide (**13c**).* Compound **13c** was obtained from the corresponding *E*-enecarbamate (**1a**,19.1 mg, 0.1 mmol) as a colorless oil (16.5 mg) in 42% yield: $[\alpha]^{23}_D$ +52.0 (*c* 0.2, $CHCl_3$); IR 3411, 3281, 1726, 1636, 1520, 1456, 1339, 1217, 1096, 742, 711 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 3.38 (br s, 1H, NH), 3.31 (br s, 1H, NH), 7.60 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, app t, *J* = 7.2 Hz, 1H), 7.37−7.26 (m, 6H), 7.17 (s, app d, *J* = 9.0 Hz, 1H, NH), 7.02 (dd, app q, *J* = 7.8 Hz, 2H), 6.90 (dd, app q, *J* = 6.6 Hz, 2H), 5.10 (q, *J* = 7.8 Hz, 1H), 4.76 (d, *J* = 9.0 Hz, 1H), 1.16 (d, *J* = 5.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$, −30 °C) $\delta$ (ppm) mixture of rotamers: 167.0 (Cq), 136.9 (2 × Cq), 135.4 (2 × Cq), 131.9 (CH), 128.9 (2 × CH), 127.7 (Cq), 127.6 (2 × CH), 123.5/122.7 (2 × CH, rot.1/rot.2), 121.9/121.8 (2 × CH, rot.1/rot.2), 119.7/119.6 (2 × CH, rot.1/rot.2), 119.2/119.1 (2 × CH, rot.1/rot.2), 116.9/116.7 (2 × Cq, rot.1/rot.2), 112.0/111.9 (2 × CH, rot.1/rot.2), 48.9 (CH), 39.8 (CH), 19.8 ($CH_3$); ESI-HRMS calcd for $C_{26}H_{24}N_3O$ $[M + H]^+$ 394.1914, found 394.1919. Enantiomeric excess is >99% determined by HPLC (Chiralpak AD-H, heptane/EtOH = 90/10, flow rate = 1.0 mL/min, 254 nm): minor isomer, $t_R$ = 21.4 min; major isomer, $t_R$ = 30.3 min.

*Benzyl N-[(2S)-1-(furan-2-yl)-2-(phenylformamido)propyl]-carbamate (**13d**).* Compound **13d** was obtained from the corresponding *E*-enecarbamate (**1a**, 19.1 mg, 0.1 mmol) as a colorless oil (18.1 mg, dr 1:2) in 48% yield: $[\alpha]^{23}_D$ +58.4 (*c* 0.5, $CHCl_3$); IR 3323, 2970, 1738, 1691, 1633, 1531, 1268, 1232, 1023, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.81−7.71 (m, 2H), 7.56−7.12 (m, 9H), 6.69 (br s, 1H, NH), 6.39−6.24 (m, 2H), 5.85 (br s, 0.2H, rot.2, NH), 5.59 (br s, 0.8H, rot.1, NH), 5.17−5.02 (m, 1H), 4.99 (s, 1H), 4.81 (d, app t, *J* = 8.7 Hz, 1H), 4.70−4.56 (m, 1H), 1.23 (d, *J* = 6.3 Hz, 0.8H, rot.2), 1.17 (d, *J* = 6.6 Hz, 2.2H, rot.1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ (ppm) mixture of diastereomers and rotamers: 167.7 (Cq), 157.1 (Cq), 142.6/142.5 (2 × CH, rot.1/rot.2), 134.3 (2 × Cq, rot.1/rot.2), 131.7/131.6 (CH, rot.1/rot.2), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.7 (2 × CH), 127.1 (2 × CH), 110.7/110.5 (CH, rot.1/rot.2), 108.1 (CH), 67.4/67.2 ($CH_2$, rot.1/rot.2), 54.7/54.2 (CH, rot.1/rot.2), 49.6 (CH), 18.5/17.3 ($CH_3$, rot.1/rot.2); ESI-HRMS calcd for $C_{22}H_{22}N_2O_4Na$ $[M + Na]^+$ 401.1472, found 401.1476. Enantiomeric excess is 98/97% determined by HPLC (Chiralpak OJ-H, heptane/EtOH = 95/5, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: major isomer, $t_R$ = 9.5 min; minor isomer, $t_R$ = 10.4 min. Minor diastereomer: minor isomer, $t_R$ = 19.1 min; major isomer, $t_R$ = 28.6 min.

*Benzyl 2-[(1S)-1-{[(Benzyloxy)carbonyl]({[(benzyloxy)carbonyl]-amino})amino}ethyl]-6-hydroxy-3-oxo-1,2,3,6-tetrahydropyridine-1-carboxylate (**14**).* To a solution of **13d** (55.7 mg, 0.1 mmol) in $CH_2Cl_2$ (1.0 mL) was added *m*-CPBA (24.6 mg, 0.11 mmol, ≤ 77%). The solution was stirred for 16 h at room temperature. The reaction was quenched with water and sodium thiosulfate aqueous solution. The aqueous layer was extracted with dichloromethane. Combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under vacuum. The crude was purified by flash chromatography on silica gel (heptane/EtOAc 6/4) to afford the desired produc as a colorless oil (49.3 mg, dr 2:1) in 86% yield. $[\boldsymbol{\alpha}]^{23}_D$ −4.4 (*c* 1.0, $CHCl_3$); IR 3450, 3033, 1703, 1397, 1304, 1267, 1214, 1133, 748, 696 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ (ppm) mixture of diastereomers and rotamers: 7.45−7.14 (m, 16H + OH), 7.02 (br s, 1H, NH), 6.92 (dd, *J* = 3.9 Hz and *J* = 3.9 Hz, 1H), 6.15−6.05 (m, 1H), 5.93 (d, *J* = 2.4 Hz, 1H), 5.44−4.81 (m, 6H), 4.79−4.62 (m, 1H), 4.60−4.41 (m, 1H), 1.27 (d, *J* = 8.4 Hz, 0.7H, dia.1, rot.1), 1.21 (d, *J* = 6.6 Hz, 1.7H, dia.1, rot.2), 1.09 (d, *J* = 6.6 Hz, 0.6H, dia.2); $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ (ppm) mixture of diastereomers and rotamers: 192.4 (Cq), 157.9 (2 × Cq), 156.2 (Cq), 146.4/146.2 (CH, rot.1/rot.2), 135.9 (Cq), 135.6 (2 × Cq), 129.4 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 127.9 (CH), 127.7 (2 × CH), 126.2 (CH), 72.3 ($CH_3$), 69.3/69.1 ($CH_2$, rot.1/rot.2), 68.8/68.6 ($CH_2$, rot.1/rot.2), 68.4/67.9 ($CH_2$, rot.1/rot.2), 65.1/65.0 (CH, rot.1/rot.2, dia.2), 61.9/61.0 (CH, rot.1/rot.2, dia.1), 56.0/55.1 (CH, rot.1/rot.2, dia.1), 53.8/52.7 (CH, rot.1/rot.2, dia.2), 14.6/13.4 ($CH_3$, rot.1/rot.2, dia.1), 13.0/12.9 ($CH_3$, rot.1/rot.2, dia.2); ESI-HRMS calcd for $C_{31}H_{31}N_3O_8Na$ $[M + Na]^+$ 596.2003, found 596.2024. Enantiomeric excess is 92/97% determined by HPLC (Chiralpak IA, heptane/*i*PrOH = 85/15, flow rate = 1.0 mL/min, 214 nm). Major diastereomer: minor isomer, $t_R$ = 59.5 min; major isomer, $t_R$ = 75.3 min. Minor diastereomer: minor isomer, $t_R$ = 32.7 min; major isomer, $t_R$ = 37.3 min.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03093.

Characterization of new compounds, selected NMR and HPLC spectra, and X-ray/ORTEP structure of **13a** (PDF)

Crystallographic data for **13a** (CIF)



DOI: 10.1021/acs.joc.6b03093
J. Org. Chem. 2017, 82, 1775−1789

## AUTHOR INFORMATION


### Corresponding Author

*E-mail: geraldine.masson@cnrs.fr.

### ORCID

Géraldine Masson: 0000-0003-2333-7047


### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank ICSN and CNRS for financial support and doctoral fellowship to A.D.

## REFERENCES


(1) For selected reviews, see: (a) Michalson, E. T.; Szmuszkovicz, J. In *Progress in Drug Research*; Springer, 1989; pp 135−149. (b) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101−114.

(2) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305−1306.

(3) Lew, W.; Chen, X.; Kim, C. U. *Curr. Med. Chem.* **2000**, *7*, 663−672.

(4) *Chiral Diazaligands for Asymmetric Synthesis*; Lemaire, M., Mangeney, P., Eds.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 2005; Vol. *15*.

(5) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627.

(6) For selected reviews, see: (a) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, *2009*, 2401−2420. (b) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887−2939.

(7) For selected examples, see: (a) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391−1394. (b) Uraguchi, D.; Nakashima, D.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7242−7243. (c) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *Synlett* **2011**, *2011*, 1265−1267. (d) Lykke, L.; Monge, D.; Nielsen, M.; Jørgensen, K. A. *Chem. - Eur. J.* **2010**, *16*, 13330−13334.

(8) For selected reviews, see: (a) Muñiz, K. *New J. Chem.* **2005**, *29*, 1371−1385. (b) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269−275. (c) De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067−4105.

(9) For selected examples, see: (a) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611−1613. (b) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084−12085.

(10) For selected examples, see: (a) Shimizu, M.; Suzuki, I.; Makino, H. *Synlett* **2003**, 1635−1638. (b) Gao, Y.; Yoshida, Y.; Sato, F. *Synlett* **1997**, *1997*, 1353−1354. (c) Matsumoto, M.; Harada, M.; Yamashita, Y.; Kobayashi, S. *Chem. Commun.* **2014**, *50*, 13041−13044.

(11) For recent reviews on electrophilic $\alpha$-amination, see: (a) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292−4300. (b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001−2011. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138−6171. (e) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917−958. (f) Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J. *Synthesis* **2014**, *46*, 2983−3003.

(12) Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7993−7995.

(13) Chang, L.; Kuang, Y.; Qin, B.; Zhou, X.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2010**, *12*, 2214−2217.

(14) (a) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94−97. (b) Lalli, C.; Dumoulin, A.; Lebée, C.; Drouet, F.; Guérineau, V.; Touboul, D.; Gandon, V.; Zhu, J.; Masson, G. *Chem. - Eur. J.* **2015**, *21*, 1704−1712.

(15) Maji, B.; Lakhdar, S.; Mayr, H. *Chem. - Eur. J.* **2012**, *18*, 5732−5740.

(16) Dumoulin, A.; Lalli, C.; Retailleau, P.; Masson, G. *Chem. Commun.* **2015**, *51*, 5383−5386.

(17) For recent reviews, see: (a) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. *ACS Catal.* **2016**, *6*, 5747−5763. (b) Kataja, A. O.; Masson, G. *Tetrahedron* **2014**, *70*, 8783−8815. For reviews on the reactivity of $\alpha$-amidoethers, see: (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon, Oxford, 1991; Vol. *2*, pp 1047−1082. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

(18) (a) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389−10392. (b) He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11088−11091. (c) Pous, J.; Courant, T.; Bernadat, G.; Iorga, B. I.; Blanchard, F.; Masson, G. *J. Am. Chem. Soc.* **2015**, *137*, 11950−11953. (d) Gelis, C.; Bekkaye, M.; Lebée, C.; Blanchard, F.; Masson, G. *Org. Lett.* **2016**, *18*, 3422−3425.

(19) Jumdar, K. C., Chattopadhyay, S. K., Eds. *Heterocycles in Natural Product Synthesis*; Wiley-VCH Verlag, 2011.

(20) Lamberth, C., Dinges, J., Eds. *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Wiley-VCH Verlag, 2012.

(21) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5859.

(22) Zillich, O. V.; Schweiggert-Weisz, U.; Eisner, P.; Kerscher, M. *Int. J. Cosmet. Sci.* **2015**, *37*, 455−464.

(23) For reviews on asymmetric aza-Friedel−Crafts reaction: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190−2201. (c) Bhadury, P.; Pang, J. *Curr. Org. Chem.* **2014**, *18*, 2108−2124.

(24) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484−1485.

(25) (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292−293. (b) Courant, T.; Kumarn, S.; He, L.; Retailleau, P.; Masson, G. *Adv. Synth. Catal.* **2013**, *355*, 836−840.

(26) For recent selected examples of $\alpha$-aminosulfides as *N*-acylimine or *N*-acyliminium precursors, see: (a) Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159−10173. (b) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235−244. (c) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167−3175. (d) Guindon, Y.; Gagnon, M.; Thumin, I.; Chapdelaine, D.; Jung, G.; Guérin, B. *Org. Lett.* **2002**, *4*, 241−244. (e) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476−12477. (f) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148−7152.

(27) George, N.; Bekkaye, M.; Alix, A.; Zhu, J.; Masson, G. *Chem. - Eur. J.* **2014**, *20*, 3621−3625.

(28) No isomerization of *trans*-**11a** into *syn*-**11a** when the trans isomer **11a** was heated between 40 and 80 °C in the presence of 50 mol% phosphoric acid **3f**, $BF_3{\cdot}OEt_2$, or NIS.

(29) Maione, F.; Cicala, C.; Musciacco, G.; De Feo, V.; Amat, A. G.; Ialenti, A.; Mascolo, N. *Nat. Prod Commun.* **2013**, *8*, 539−544.

(30) Mayr's scale for furane and 1,3-dimethoxybenzene: (a) Ammer, J.; Nolte, C.; Mayr, H. *J. Am. Chem. Soc.* **2012**, *134*, 13902−13911. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500−9512.

(31) Selected examples of formation of bis-indoles: (a) Jia, Y.; Xie, J.; Duan, H.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 1621−1624. (b) Esquivias, J.; Arrayas, R. M.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629−633. (c) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 557−559.

(32) For selected examples, see: (a) Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* **2001**, *2001*, 1443−1445. (b) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629−633. (c) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, *2010*, 47−50. (d) Xiu, W.; Zhenhua, W.; Zhang, G.; Zhang, W.; Wu, Y.; Gao, Z. *Eur. J. Org. Chem.* **2016**, *2016*, 502−507.

(33) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250−2293.

(34) For selected examples, see: (a) Yang, C.; Liao, L.; Xu, Y.; Zhang, H.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **1999**, *10*, 2311−2318.




DOI: 10.1021/acs.joc.6b03093
*J. Org. Chem.* 2017, 82, 1775−1789

(b) Harris, J. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 2029−2031. (c) Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591−8601.
(35) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, *1998*, 105−114.
(36) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240−1243.
(37) (a) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023−6026. (b) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802−14803. (c) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790−3791.



DOI: 10.1021/acs.joc.6b03093
*J. Org. Chem.* 2017, 82, 1775−1789