Bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]-carbodiimide (BDDC) and Its Application to Residue-Free Esterifications, Peptide Couplings, and Dehydrations

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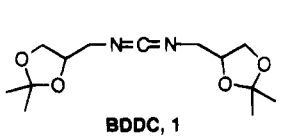
Introduction

Carbodiimides are important reagents in synthetic chemistry and are employed in a wide variety of transformations,[1] generally functioning as dehydrating agents. Carbodiimides such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and 1-(3-(dimethylamino)-propyl)-3-ethylcarbodiimide hydrochloride (EDC) are used primarily as peptide coupling reagents and are employed less frequently for direct *O*-acylations. A major problem is the use of carbodiimides such as DCC or DIC has been the frequently encountered difficulty of separating the desired reaction product from the neutral urea formed as a result of the dehydration and still retained with the organic material. EDC and other "water soluble" carbodiimides[2] have largely addressed this issue, as the resulting urea byproducts formed from the dehydration reaction are basic and can be easily removed with a dilute acid wash.

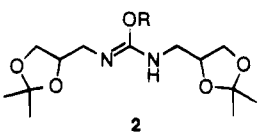
Such carbodiimides bearing charged or basic amino groups, however, are ineffective for esterifications which depend on initial protonation of the carbodiimide moiety. In ester formation, carbodiimides such as DCC and DIC have been used infrequently as direct *O*–acylating agents, due in part to the formation of undesirable *N*-acylurea as well as the accompanying urea which can complicate purification. In cases where very mild, neutral esterification conditions are required, due to substrate sensitivity to acidic or basic reaction environments, isoureas formed from carbodiimides are ideal and have been successfully employed.[3] Formed from the CuCl-catalyzed addition of an alcohol to a carbodiimide, isoureas yield a wide variety of esters under mild, racemization-free[4] conditions.

We have found an important and broadly applicable use of isoureas to be the introduction of *tert*-butyl esters. The *tert*-butyl ester is a versatile synthetic protecting group, easily removed under nonracemizing acid conditions and orthogonal to many other *N*- and *O*-protecting groups. The substantial steric bulk of a *tert*-butyl ester also contributes to a temporary stereo-directing group, one that we have exploited frequently.[5] Many methods have been reported for the synthesis of *tert*-butyl esters,[6] a number of which rely on strong acids, bases, or expensive and toxic reagents. In our hands *N,N'*-diisopropyl-*O-tert*-butylisourea has been the reagent of choice for the introduction of the *tert*-butyl ester into a variety of *N*-protected amino acids and derivatives. This reagent gives good yields of *tert*-butyl esters (75–90%),[7] but has several drawbacks. The formation of isourea proceeds slowly and in only moderate yield and requires CuCl to catalyze the conversion. The resulting reaction mixture must be washed, filtered, and distilled to obtain acceptably pure reagent. Removal of the residual *N,N'*-diisopropylurea formed in the esterification reaction from the target ester can be difficult and chromatography is often necessary.

With these shortcomings in mind, we sought to design a new carbodiimide which would have neutral alkyl substituents, form isoureas in good yield and high purity, be symmetrical,[8] and give reaction residues, including the corresponding isourea and urea, that would be readily removed from the organic product. We now report the synthesis and chemistry of bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC, **1**) and that of several of its isourea derivatives **2**. We have found **1** to be a superior reagent for the formation of isoureas, especially *tert*-butylisourea derivative **2** (R = Bu^t), as well as being an effective peptide coupling reagent and general dehydration agent. The isoureas **2** and corresponding urea **3** formed from **1** are efficiently washed from organic mixtures with dilute acids such as 0.1 N HCl or phosphoric acid, since they have significant distribution into the aqueous phase from an organic solvent. Once in the water phase, the propanediol isopropylidene ketal side chains rapidly hydrolyze to reveal the very hydrophilic tetrol **4** and make the extraction total. The neutrality of the propanediol isopropylidene ketal side chains allows for enhanced organic solubility, ease of isourea formation, and use. Also, **1** is easily prepared on a 200–300 g scale and is a readily distilled, stable,[9] nonvolatile reagent.



BDDC, 1



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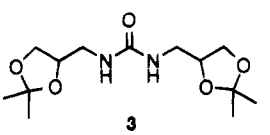

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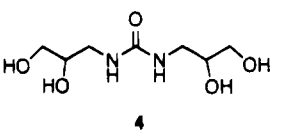

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Results and Discussion

The synthesis and application of BDDC (**1**) is dependent on an efficient route to 1-amino-2,3-propanediol isopropylidene ketal (**6**). Amine **6** had been previously obtained from the high pressure aminolysis of tosylate **5**[10] in good yield, and this constitutes an excellent method for the large scale preparation of **6**. Avoiding the high

(1) (a) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589. (b) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233. (c) Kurzer, F.; Douraghi-Zadeh, D. *Chem. Rev.* **1967**, *67*, 107.

(2) Sheehan, J. C.; Hlavka, J. J. *J. Org. Chem.* **1955**, *21*, 439.

(3) Mathias, L. *Synthesis* **1979**, 561.

(4) This has been established by HPLC in our laboratory.

(5) For several examples, see Hernandez, A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 1058, and ref 15 therein.

(6) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc., 1991, 245. (b) Chevallet, P.; Garrouste, P.; Malawska, B.; Martinez, J. *Tetrahedron Lett.* **1993**, *34*, 7409. (c) Nagasawa, K.; Ohhashi, K.; Yamashita, A.; Ito, K. *Chem. Lett.* **1994**, 209.

(7) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216, and references therein.

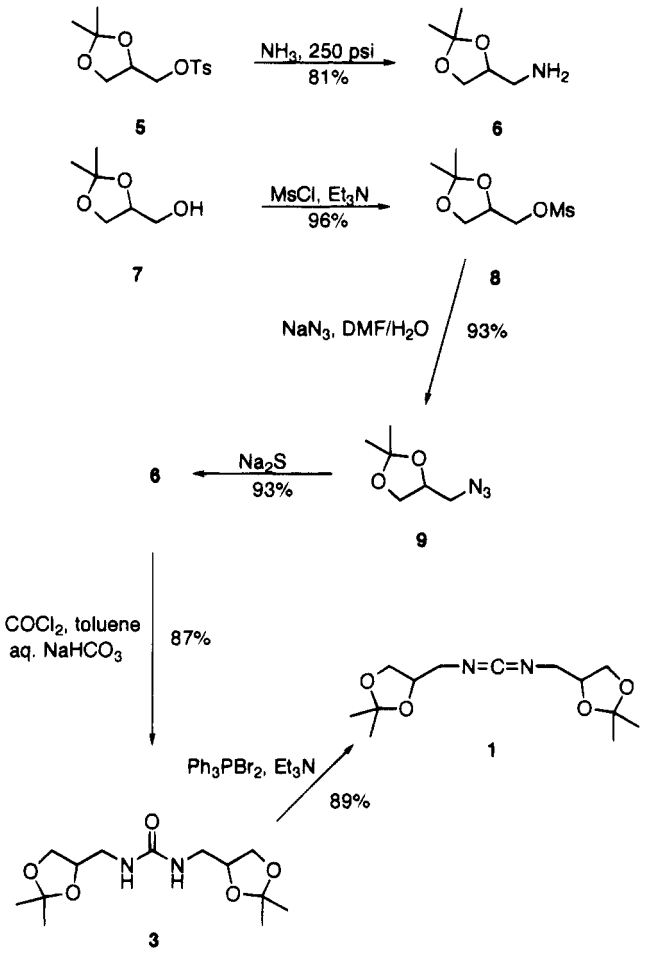
(8) A symmetrical carbodiimide (where R = R') would be more easily synthesized than an unsymmetrical carbodiimide, and therefore less costly to produce.

(9) TLC, IR, NMR, and C,H,N analyses indicated no change in the quality of **1** after storage for six months at 0 °C under argon.

(10) Green, M. M.; Gross, R. A.; Crosby, C., III; Schilling, F. C. *Macromolecules* **1987**, *20*, 992.

0022-3263/94/1959-7503$04.50/0

Scheme 1. Synthesis of Carbodiimide 1



pressure equipment required for the direct conversion of **5** to **6**, we converted **5** or mesylate **8** to the corresponding azide **9** which could then be easily reduced to **6** (Scheme 1). The production of amine **6** began with the large scale conversion of solketal (**7**) to **8** with MsCl and Et_3N in CH_2Cl_2 in 96% yield. Mesylate **8** then was heated with NaN_3 in DMF/H_2O to give azide **9**, typically in >90% yield. Reduction of azide **9** to amine **6** was initially carried out with 10% Pd/C in MeOH under a hydrogen atmosphere, but this was changed to Na_2S[11] in warm MeOH/H_2O for speed and safety reasons. Reduction with Na_2S was complete in 24 h, whereas catalytic reduction took several days. Amine **6** was consistently obtained from **9** in >90% yield, thus in about 80% overall yield from **7**. Dropwise addition of a freshly prepared $COCl_2$/toluene solution to amine **6** in a vigorously stirred toluene/aqueous $NaHCO_3$ mixture at 0 °C gave crystalline urea **3** in 87% yield. Facile conversion of **3** to BDDC (**1**) was accomplished using $Ph_3P{\cdot}Br_2$[12] and Et_3N in CH_2Cl_2 in 85–90% distilled yield.

With a supply of **1** in hand, we investigated its usefulness as a source of isoureas for esterification, primarily as a method to introduce *tert*-butyl esters. Reaction of **1** at rt with 400 mol % of *tert*-butyl alcohol and 1–2 mol % of freshly prepared CuCl gave a quantitative yield of analytically pure *tert*-butylisourea **2** (R = Bu^t) in less than 1 h. The reaction was monitored using IR by following the disappearance of the carbodiimide absorption at 2130 cm^{-1} and the appearance of the isourea absorbance at 1660 cm^{-1}. No purification other than evaporation of the excess *tert*-butyl alcohol was necessary to obtain the pure material. Isourea **2** (R = Bu^t) was then stirred with *N*-CBZ-Ala (**10**) in several solvents under a variety of reaction conditions to determine the most effective conditions for *tert*-butyl ester formation. In general, all the solvents examined gave reasonable yields of *N*-CBZ-Ala-OBu^t (**15**), but warm toluene, overnight, produced the best results. Several other *N*-BOC protected amino acids were treated with **2** (R = Bu^t) and gave good yields of *tert*-butyl esters under similar conditions (Table 1). In each example, the yields were comparable if not slightly superior to those obtained using the *O-tert*-butylisourea of DIC, which gave yields in the range of 75–90% but required chromatography to obtain a pure product.[7] Esterification of the racemization sensitive CBZ-Ala-Phe (**11**) with **2** (R = Bu^t) gave the *tert*-butyl ester **20**, shown by HPLC analysis to be a single diastereomer. Esterification of **11** using K_2CO_3 and *tert*-butyl bromide in DMA[6b] gave **20** with 2.5% racemization to the L,D diastereomer. Other isourea derivatives **2** (R = Bn, Pr^i, Et, Me) of **1** were synthesized, with results identical to that of **2** (R = Bu^t) in yields and ease of purification. Each isourea was formed rapidly and quantitatively at rt with 1–2 mol % CuCl and only a slight excess of alcohol. The quality of the CuCl catalyst was important, as older samples gave slower reactions and were required in up to 5 mol %. Surprisingly, each isourea, including the Bu^t, could be produced quantitatively without the use of catalytic CuCl, although heating and longer reaction times were required. In the case of DIC, no isourea was obtained without catalytic CuCl and with EDC no isourea at all was formed with or without CuCl. All our results indicated that the presence or absence of the CuCl had no effect on subsequent esterifications.

Table 1. Ester Formation Using BDDC-Derived Isoureas 2

substrate	conditions	**2**, R	ester product	yield, %
CBZ-Ala (**10**)	toluene, 85 °C, 20 h	Bu^t	**15**	94
10	THF, 45 °C, 20 h	Bn	**16**	92
10	THF, reflux, 16 h	Pr^i	**17**	87
10	DMF, rt, 16 h	Et	**18**	81
10	DMF, rt, 16 h	Me	**19**	93
CBZ-Ala-Phe (**11**)	toluene, 85 °C, 14 h	Bu^t	**20**	87[a]
11	DMF, rt, 20 h	Me	**21**	82[a]
bis-BOC-Orn (**12**)	toluene, 80 °C, 20 h	Bu^t	**22**	86
bis-BOC-His (**13**)	toluene, 80 °C, 20 h	Bu^t	**23**	77
BOC-Pro (**14**)	toluene, 80 °C, 20 h	Bu^t	**24**	90

[a] HPLC analysis of the product indicated less than 0.1% of the L,D diastereomer present.

The removability of isoureas **2** and urea **3** was examined during isolation of the esterification products. Dilution with EtOAc, two washes with 1 M HCl followed by one with aqueous bicarbonate gave pure product ester after evaporation of the organic solvent, as judged by NMR, TLC and mass balance. Both NMR and TLC showed the absence of any **2** or **3** in the organic phase. A more precise measurement of the acid extractability of **1** and its derivatives **2** and **3** was made by dissolving a measured quantity of each in an organic solvent (ethyl acetate, dichloromethane, or toluene), extracting with aqueous acid (HCl or H_3PO_4), and weighing the residue left after evaporation of the organic solvent. Each of the compounds tested was removed to the extent of >99% after two acid washes, regardless of the organic solvent. Acid no more than 0.1 M was sufficient to remove most

(11) Belinka, B. A., Jr.; Hassner, A. *J. Org. Chem.* **1979**, *44*, 4712.
(12) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373.

Table 2. Peptide Couplings Using BDDC (1)[a]

substrate	amine salt	solvent, time, h	coupled product	yield (L,D)[b] %
CBZ-Ala (**10**)	Phe-OMe·HCl	THF, 24	**21**	84
10	Phe-OMe·HCl	DMF, 24	**21**	93
BOC-Ile (**25**)	Phe-OMe·HCl	THF, 16	**26**	82
25	Phe-OMe·HCl	DMF, 16	**26**	84
CBZ-Ala-Phe (**11**)	Gly-OBn·TsOH	DMF, 4	**27**	81 (0.68)
11	Gly-OBn·TsOH	DMF, 20	**27**	91 (1.3)
11	Gly-OBn·TsOH	DMF, 4[c]	**27**	71 (<0.1)
11	Gly-OBn·TsOH	DMF, 20[c]	**27**	78 (<0.1)

[a] All reactions were conducted at rt using *N*-methylmorpholine and HOBT. [b] The analytical limit for detection of L,D diastereomers is 0.1%. [c] With 50 mol % of anhydrous $CuCl_2$.

reagent residues. Even water (pH 7) removed greater than 80% of residual mass after only two washes; **1** and its derivatives clearly possessed the necessary solubility properties.

Having established the removability of **1** and its derivatives from organic solvents, we next investigated its effectiveness as a peptide coupling reagent (Table 2) and general dehydrating agent. Coupling CBZ-Ala (**10**) and Phe-OMe·HCl in THF with HOBT and **1** afforded CBZ-Ala-Phe-OMe (**21**) in 84% yield. Using DMF as the solvent, the yield increased to 93%. The more hindered coupling of BOC-Ile (**25**) and Phe-OMe·HCl with HOBT and **1** produced yields of 82 and 85% of BOC-Ile-Phe-OMe (**26**) in THF and DMF, respectively. In all cases there was no racemization, as would be expected for *N*-carbamate-protected amino acids. The **1**/HOBT-mediated C-terminus coupling of CBZ-Ala-Phe (**11**) with Gly-OBn·TsOH in DMF produced CBZ-Ala-Phe-Gly-OBn (**27**) in which the Phe was racemized to the extent of 0.68% after 4 h and 1.3% after 20 h. The same results were obtained when these components were coupled with EDC and DCC,[13] although the products using the latter reagent required chromatographic purification. Coupling carried out in the presence of 50 mol % of anhydrous $CuCl_2$ gave racemization-free **27**, even after reactions were allowed to proceed for 20 h at rt. These results are also in agreement with literature data.[13a,b] In each case, all residual **1** and urea byproducts **3** were easily removed from the reaction mixtures with a simple acid wash.

Finally, **1** was examined as a potential general dehydrating agent. Benzyl 3-hydroxybutanoate was heated with **1** and 5 mol % of fresh CuCl. This produced benzyl crotonate in 83% yield.

Conclusion

A new, readily, synthesized carbodiimide, BDDC (**1**), is useful for racemization-free esterifications and peptide couplings and for dehydrations. The uniquely hydrophilic properties of carbodiimide **1** and its isourea derivatives allow for easy removal from organic reaction media with simple dilute acid extraction, leaving the desired products free of carbodiimide-derived reaction byproduts.

Experimental Section

All moisture sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Toluene, *tert*-butyl alcohol, DMF, triethylamine, and dichloromethane were distilled from CaH_2; THF was distilled from sodium benzophenone ketyl; NMM was distilled prior to use, and stored under nitrogen. Anhydrous CuCl was prepared by the method of Keller.[14] Anhydrous $CuCl_2$ was prepared by heating $CuCl_2{\cdot}2H_2O$ at 100 °C and 0.1 Torr for 24 h. IR spectra were recorded as thin films with absorptions reported in cm^{-1}. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ using TMS as an internal reference unless otherwise noted. ^{13}C NMR spectra were recorded at 75 MHz. All chemical shifts (δ) are reported in ppm and coupling constants are in hertz. Melting points are uncorrected. Final organic extracts were dried over Na_2SO_4.

Solketal Mesylate (8). Solketal (**7**, 250 g, 1.8 mol) and triethylamine (300 mL, 217 g, 120 mol %) were dissolved in 750 mL of dichloromethane and cooled to 0 °C. Mesyl chloride (163 mL, 241 g, 115 mol %) was added over 1.5 h to the vigorously stirred solution. The reaction mixture was allowed to stir for an additional 15 h at rt after addition of mesyl chloride had been completed. The resulting slurry was washed with 3 × 200 mL portions of saturated aqueous sodium bicarbonate, followed by 3 × 200 mL portions of water. The organic layer was dried, filtered, and evaporated to an orange oil, mesylate **8** (379 g, 96%), which was converted to azide **9** without further purification: ^1H NMR δ 4.30–4.28 (m, 1H), 4.12 (d, 2H, J = 5.5), 4.01 (dd, 1H, J = 6.5, 8.8), 3.76 (dd, 1H, J = 5.7, 8.9), 2.98 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H). Anal. Calcd for $C_7H_{14}O_5S$: C, 40.0; H, 6.7. Found: C, 39.7; H, 6.7.

1-Azido-2,3-propanediol Isopropylidene Ketal (9). Mesylate **8** (376 g, 1.79 mol) was dissolved in 488 mL of DMF, followed by the addition of sodium azide (137 g, 120 mol %) in 440 mL of water and the resulting mixture was heated at 110 °C for 6 h; TLC analysis indicated complete consumption of **8**. The reaction mixture was cooled to rt, 400 mL of saturated brine was added, and the solution was extracted with 5 × 400 mL portions of ether, after which the extracts were combined and concentrated to approximately 1 L. The resulting organic solution was washed with 2 × 200 mL portions of water, dried, and then evaporated to a yellow oil, azide **9** (325 g, 93%). This material was reduced to amine **6** without further purification: IR 2100; ^1H NMR δ 4.21–4.15 (m, 1H), 3.97 (dd, 1H, J = 6.4, 8.3), 3.70 (dd, 1H, J = 6.0, 8.3), 3.32 (dd, 1H, J = 4.6, 12.6), 3.21 (dd, 1H, J = 5.6, 12.6), 1.40 (s, 3H), 1.31 (s, 3H).

1-Amino-2,3-Propanediol Isopropylidene Ketal (6). Azide **9** (192 g, 1.22 mol) was dissolved in 260 mL of CH_3OH. This solution was added to a solution of $Na_2S(H_2O)_9$ (367 g, 125 mol %) in 573 mL of H_2O and the two-phase mixture was heated to 55 °C and stirred at that temperature for 24 h, leaving the mixture open to the atmosphere as N_2 evolved. The resulting homogeneous orange solution was saturated with NaCl and extracted with 7 × 200 mL portions of ether, and the ether was dried, filtered, and evaporated to yield a viscous orange oil. This oil was distilled at reduced pressure (23–28 °C/1 Torr) to give 149 g of **6**, 93% yield: IR 3400, 3300; ^1H NMR δ 4.19–4.11 (m, 1H), 4.04 (dd, 1H, J = 7.8, 6.5), 3.68 (dd, 1H, J = 8.0, 6.4), 2.89–2.75 (m, 2H), 2.95 (s, 2H), 1.42 (s, 3H), 1.39 (s, 3H). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.9; H, 10.0; N, 10.7. Found: C, 54.9; H, 9.7; N, 10.6.

***N,N'*-Bis[[4-(2,2-Dimethyl-1,3-dioxolyl)]methyl]urea (3).** A solution of amine **6** (149 g, 1.14 mol) in toluene (680 mL) was added to a solution of $NaHCO_3$ (192 g, 200 mol %) in 680 mL of H_2O. This two-phase mixture was cooled to 0 °C and vigorously stirred as a freshly prepared solution of phosgene in toluene (231 mL, 2.46 M solution, 50 mol %) was added dropwise over 2 h. The reaction mixture was allowed to stir at rt for an additional 16 h, the layers were separated, and the toluene was dried, filtered, and evaporated to give a white solid residue. The water layer was extracted with 3 × 300 mL portions of EtOAc, and the combined organics were dried and evaporated. The combined residual white solids were recrystallized from toluene/hexane to afford 142 g (87%) of urea **3**: mp 108–110 °C; IR 3350, 1640, 1570; ^1H NMR δ 5.42 (br s, 2H), 4.26–4.19 (m, 2H), 4.08–4.00 (m, 2H), 3.71–3.62 (m, 2H), 3.56–3.41 (m, 2H), 3.29–3.18 (m, 2H), 1.41 (s, 6H), 1.38 (s, 6H); ^{13}C NMR δ 158.6, 109.1, 75.3,

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(14) Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.

(15) Moriniere, J. L.; Danree, B.; Lemoine, J.; Guy, A. *Synth. Commun.* **1988**, *18*, 44.

66.5, 42.6, 26.7, 25.2. Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.2; H, 8.4; N, 9.7. Found: C, 54.3; H, 8.7; N, 9.8.

Bis[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide (BDDC, 1). Triphenylphosphine (131 g, 110 mol %) was dissolved in 1.1 L of dry dichloromethane, and the resulting solution was cooled to 0 °C. Bromine (25.7 mL, 80 g, 110 mol %) was added dropwise over 15 min, and then triethylamine (157 mL, 114 g, 250 mol %) was added in one portion. Solid urea **3** (131 g, 0.45 mol) was added to the yellow suspension in small portions over 50 min. The resulting brown slurry was stirred at rt for an additional 3 h, the reaction mixture was diluted with 500 mL of hexane, the solids were filtered off and washed with ether, and the washings were combined with the filtrate. The combined organic phase was evaporated to a brown slurry which then was resuspended in fresh ether and again diluted with hexane, and the solids were filtered off and washed with ether. The procedure of evaporation, suspension, and filtration is repeated until no further solids precipitate (usually four cycles). The final viscous, clear brown oil, crude **1**, was distilled bulb to bulb at reduced pressure to give pure **1** as a pale yellow oil, 107 g, 89% yield, which could be stored indefinitely at 0 °C under argon:[9] bp 115–125 °C, 0.3 min; IR 2130; ^{1}H NMR δ 4.15–4.10 (m, 2H), 3.98 (dd, 2H, J = 6.2, 8.3), 3.68 (dd, 2H, J = 5.8, 8.3), 3.31 (dd, 2H, J = 5.6, 12.8), 3.24 (dd, 2H, J = 5.8, 12.8), 1.39 (s, 6H), 1.29 (s, 6H); ^{13}C NMR δ 139.6, 109.2, 74.8, 66.7, 48.6, 26.6, 25.1. Anal. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.8; H, 8.2; N, 10.4. Found: C, 58.0; H, 8.1; N, 10.7.

General Procedure for the Synthesis of Isoureas 2. The synthesis of *O-tert*-butylisourea **2** is representative. Compound **1** (5 g, 18.5 mmol) was stirred with 400 mol % of *tert*-butyl alcohol (5.5 g) and 2 mol % of freshly prepared CuCl (30 mg) at rt for 1 h. IR data indicated complete conversion of **1** to isourea **2** (disappearance of the carbodiimide absorption at 2130 and appearance of the isourea absorbance at 1665 cm^{-1}). Excess *tert*-butyl alcohol was removed under reduced pressure to leave a dark green semisolid residue, 6.41 g, 99%, which by NMR was a single product, **2**, that was analytically pure; **2** was also produced without the use of CuCl but required heating at 70 °C for 24 h. The product **2** obtained was identical in yield and purity to **2** synthesized using CuCl: IR 3380, 1665; ^{1}H NMR δ 5.12–5.03 (m, 1H), 4.36–2.95 (m, 10H), 1.50–1.24 (m, 21H). Anal. Calcd for $C_{17}H_{32}N_2O_5$: C, 59.3; H, 9.4; N, 8.1. Found: C, 59.2; H, 9.1; N, 8.1.

***O*-Benzylisourea 2.** Carbodiimide **1**, benzyl alcohol, and CuCl were treated according to the general procedure to give **2** (R = Bn) as a green oil; isourea **2** (R = Bn) could also be synthesized without using CuCl by heating **1** and benzyl alcohol (200 mol %) at 80 °C for 24 h: IR 3390, 3050, 1660; ^{1}H NMR δ 7.40–7.23 (m, 5H), 5.14–5.10 (m, 1H), 4.71 (s, 2H), 4.45–3.11 (m, 10H), 1.57–1.20 (m, 12H). Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.5; H, 8.0; N, 7.4. Found: C, 63.7; H, 8.0; N, 7.1.

***O*-Isopropylisourea 2** was prepared from **1** with 2-propanol and CuCl according to the general procedure to give **3** (R = Pr^i, as a dark green oil, which was used without further purification: IR 3380, 1660; ^{1}H NMR δ 5.12–5.03 (m, 1H), 4.36–3.18 (m, 11H), 1.41 (s, 12H), 1.39–1.20 (m, 6H). Anal. Calcd for $C_{16}H_{30}N_2O_5$: C, 58.2; H, 9.1; N, 8.5. Found: C, 57.8; H, 8.9; N, 8.4.

***O*-Ethylisourea 2** was prepared from **1** with ethanol and CuCl according to the general procedure to give **2** (R = Et) quantitatively as a dark green oil: IR 3400, 1660; ^{1}H NMR δ 5.13–5.10 (m, 1H), 4.30–4.20 (m, 2H), 4.11 (q, 2H, J = 7.1), 4.10–4.00 (m 2H), 3.81–3.80 (m, 1H), 3.77–3.68 (m, 1H), 3.40–3.11 (m, 4H), 1.43 (s, 6H), 1.39 (s, 6H), 1.24 (t, 3H, J = 7.1). Anal. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.9; H, 8.9; N, 8.9. Found: C, 56.6; H, 8.5; N, 8.7.

***O*-Methylisourea 2** was prepared from **1** with methanol and CuCl according to the general procedure to give **2** (R = Me) quantitatively as a dark green oil: IR 3400, 1665; ^{1}H NMR δ 5.12–5.11 (m, 1H), 4.30–4.20 (m, 2H), 4.10–4.00 (m, 2H), 3.92 (s, 3H), 3.82–3.80 (m, 1H), 3.75–3.68 (m, 1H), 3.40–3.11 (m, 4H), 1.44 (s, 6H), 1.37 (s, 6H). Anal. Calcd for $C_{14}H_{26}N_2O_5$: C, 55.6; H, 8.7; N, 9.3. Found: C, 55.5; H, 8.5; N, 8.9.

General Isolation Procedure for Reactions Using BDDC (1) Isourea Derivatives 2. Upon completion of the reaction, the reaction mixture is diluted with an appropriate organic solvent, typically ether, EtOAc, or dichloromethane. The organic layer is vigorously shaken for 2 min with two equal volumes of dilute aqueous acid (0.1–1.0 M HCl or H_3PO_4 being representative), followed by a single wash with saturated aqueous bicarbonate and finally water. The organic layer is dried, filtered, and evaporated to yield the desired product free of carbodiimide derivatives and byproducts (urea).

General Procedure for *tert*-Butyl Ester Formation Using Isourea 2 (10, (R = Bu^t). The synthesis of **CBZ-alanine *tert*-butyl ester (15)** is representative. CBZ-Ala (223 mg, 1 mmol) was dissolved in 10 mL of dry toluene, 350–400 mol % of isourea **2** (R = Bu^t, 1.72 g) was added, and the resulting solution was heated at 80–85 °C for 20 h. The mixture was evaporated and isolation was effected according to the general procedure to give *tert*-butyl ester **15** (263 mg, 94%) as a clear, fairly mobile oil: $[\alpha]^{25}_D$ −23.8° (*c* 3.6, EtOH); IR 3340, 3060, 3030, 1725; ^{1}H NMR δ 7.40–7.28 (m, 5H), 5.47 (d, 1H, J = 6.7), 5.09 (s, 2H), 4.25 (t, 1H, J = 7.3), 1.44 (s, 9H), 1.35 (d, 3H, J = 7.1). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0. Found: C, 64.2; H, 7.6; N, 5.0.

***N,N'*-Bis-BOC-Ornithine *tert*-butyl ester (22)** was synthesized from *N,N'*- bis-BOC-ornithine (**12**) according to the general procedure: yield, 86%; mp 80–82 °C: $[\alpha]^{25}_D$ +11.3° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 5.07 (br d, 1H, J = 7.8), 4.63 (m, 1H), 4.16 (t, 1H, J = 6.9), 3.14 (t, 2H, J = 6.0), 1.82–1.50 (m, 4H), 1.45 (s, 9H), 1.43 (s, 18H). Anal. Calcd for $C_{19}H_{36}N_2O_6$: C, 58.7; H, 9.3; N, 7.2. Found: C, 58.7; H, 9.7; N, 7.2.

***N*-BOC-Proline *tert*-butyl ester (24)** was synthesized from *N*-BOC proline (**14**) according to the general procedure: yield, 90%; $[\alpha]^{25}_D$-50.5° (*c* 3.4, $CHCl_3$); ^{1}H NMR δ 4.12 (dd, 1H, J = 3.4, 8.9), 3.60–3.39 (m, 2H), 2.29–2.16 (m, 1H), 2.00–1.80 (m, 3H), 1.51 (s, 9H), 1.46 (s, 9H). Anal. Calcd for $C_{14}H_{26}NO_4$: C, 61.7; H, 9.6; N, 5.1. Found: C, 61.7; H, 9.6; N, 5.4.

***N*$^\alpha$,*N*$^\tau$-Bis-BOC-histidine *tert*-butyl ester (23)** was synthesized from *N*$^\alpha$, *N*$^\tau$-bis-BOC-histidine (**13**) according to the general procedure: yield, 77%; mp 97–98 °C; $[\alpha]^{25}_D$ +17.8° (*c* 1.3, $CHCl_3$); IR 3880, 1750, 1710 cm^{-1}; NMR δ 7.98 (d, 1H, J = 0.8), 7.13 (s, 1H), 5.59 (br d, 1H, J = 8.4), 4.43 (dd, 1H, J = 2.9, 5.1), 3.00 (d, 2H, J = 5.2). Anal. Calcd for $C_{20}H_{34}N_3O_6$: C, 58.2; H, 8.3; N, 10.1. Found: C, 58.6; H, 8.2; N, 10.1.

CBZ-Ala-Phe-OBu^t (20). CBZ-Ala-Phe (**11**, 0.1 g, 0.27 mmol) and isourea **2** (R = Bu^t, 0.56 g, 400 mol %) were combined in 5 mL of dry toluene and heated at 85 °C for 14 h. Isolation proceeded as in the general procedure to give 100 mg, 87% yield, of **20** as a white solid. HPLC analysis (EtOAc/hexanes, 1/1, 1 mL/min) of the crude reaction mixture indicated <0.1% racemization: mp 119–120 °C; $[\alpha]^{25}_D$ −15.0° (*c* 1.0, EtOH); ^{1}H NMR δ 7.45–7.20 (m, 10H), 6.42 (d, 1H, J = 6.8), 5.27 (d, 1H, J = 6.9), 5.10–5.06 (m, 2H), 4.72 (m, 1H), 4.24–4.22 (m, 1H), 3.08 (d, 2H, J = 5.5), 1.40 (s, 9H), 1.34 (d, 3H, J = 7). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.6; H, 7.1; N, 6.6. Found: C, 67.6; H, 7.1; N, 6.5.

CBZ-Alanine Benzyl Ester (16). CBZ-Ala (**10**, 0.825 g, 0.0037 mol) was added to a solution of **2** (R = Bn, 2.8 g, 200 mol %) in 15 mL of THF. The reaction was heated at 45 °C for 20 h, after which the reaction was cooled and evaporated and following the general procedure gave **16** as a clear oil, 1.07 g, 92%: $[\alpha]^{25}_D$ −31.7° (*c* 1.1, EtOH); IR 3340, 3060, 3030, 1720; ^{1}H NMR δ 7.45–7.28 (m, 10H), 5.43 (d, 1H, J = 7), 5.15–5.08 (m, 4H), 4.43–4.40 (m, 1H), 1.38 (d, 3H, J = 7.1). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 69.3; H, 6.2; N, 4.7.

CBZ-Ala-OPr^i (17). CBZ-Ala (**10**, 0.46 g, 2 mmol) was dissolved in 15 mL of dry THF. Isopropylisourea **2** (4 g, 600 mol%) was added and the reaction mixture was stirred for 16 h at reflux. Following the general procedure gave 0.475 g of **17**, 87%, as a viscous oil: $[\alpha]^{25}_D$ +1.3° (*c* 1.0, $CHCl_3$); IR 3340, 3060, 3030, 1720; ^{1}H NMR δ 7.32–7.26 (m, 5H), 5.73 (d, 1H, J = 7.5), 5.08 (s, 2H), 5.03–4.99 (m, 1H), 4.32–4.28 (m, 1H), 1.35 (d, 3H, J = 7.2), 1.22 (d, 6H, J = 6.0). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.3; H, 7.2; N, 5.3. Found: C, 63.2; H, 7.4; N, 5.6.

CBZ-Ala-OEt (18). CBZ-Ala (**10**, 0.165 g, 0.74 mmol) was added to 6 mL of dry DMF containing 1.12 g (500 mol %) of **2** (R = Et), and the mixture was stirred at rt for 16 h. Following the general procedure gave 0.151 g of **18**, 81%, as an oil: $[\alpha]^{25}_D$ −32.2° (*c* 1.0, MeOH) [lit.[15] $[\alpha]^{25}D$ −32.0° (*c* 1.0, MeOH)] IR 3350, 3060, 3030, 1720; ^{1}H NMR δ 7.34–7.26 (m, 5H), 5.53 (d, 1H, J = 7.2), 5.10 (s, 2H), 4.39 (t, 1H, J = 7.3), 4.11 (q, 2H, J = 7.1) 1.40 (d, 3H, J = 7.2), 1.23 (t, 3H, J = 7.3).

CBZ-Ala-OMe (19). CBZ-Ala (**10**, 0.165 g, 0.74 mmol) was added to 6 mL of dry DMF containing 1.1 g (500 mol %) of **2** (R

= Me) and the reaction mixture was stirred for 16 h at rt. Following the general procedure gave 0.163 g of **19**, 93%, as an oil: $[\alpha]^{25}_D$ −32.7° (*c* 1.3, MeOH) [lit.[15] $[\alpha]^{25}_D$ −33.0° (*c* 1.0, MeOH)]; IR 3340, 3060, 3030, 1720; ^{1}H NMR δ 7.34−7.26 (m, 5H), 5.53 (d, 1H, *J* = 5.9), 5.10 (s, 2H), 4.39 (t, 1H, *J* = 7.3), 3.73 (s, 3H), 1.40 (d, 3H, *J* = 7.2).

CBZ-Ala-Phe-OMe (21). Phenylalanine methyl ester hydrochloride (0.5 g, 2.3 mmol) was suspended in 10 mL of dry THF. Et_3N (0.35 mL, 2.5 mol) was added, after which both CBZ-Ala (**10**, 0.52 g, 100 mol %) and **1** (0.65 g, 104 mol %) were also added. The reaction mixture was stirred for 24 h at rt. Following the general isolation procedure gave **21**, 0.74 g, 84%, as a crystalline solid. An identical reaction using DMF as the solvent produced **21** in 93% yield: mp 97−98 °C from THF/hexanes; $[\alpha]^{25}_D$ −8.3° (*c* 0.3, EtOH); ^{1}H NMR δ 7.42−7.15 (m, 10H), 6.40 (d, 1H, *J* = 4), 5.24−5.21 (m, 1H), 5.10 (s, 2H), 4.88−4.84 (m, 1H), 4.24−4.21 (m, 1H), 3.78 (s, 3H), 3.16−3.13 (m, 2H), 1.38 (d, 3H, *J* = 7). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.5; H, 6.3; N, 7.3. Compound **21** was also synthesized from the reaction of **11** and isourea **2** (R = Me) in DMF (82% yield) and was identical (HPLC, EtOAc/hexanes, 1/2, 1 mL/min) to material formed above.

CBZ-Ala-Phe-OH (11). To methyl ester **21** (1.64 g, 4.27 mmol) dissolved in 25 mL of THF and cooled to 0 °C was added $LiOH{\cdot}H_2O$ (0.25 g, 140 mol %) dissolved in 8 mL of water. The resulting solution was cooled to 0 °C, stirred for 0.5 h, and then poured into 50 mL of saturated aqueous bicarbonate. The basic mixture was then extracted with 50 mL of ether which was discarded. The water layer was acidified with 1 N HCl to pH 2 and extracted with 2 × 100 mL of ether. The organic extracts were combined, dried, and evaporated to give a thick white foam, which was crystallized from THF/hexane affording 1.53 g, 97%, of **11** as a white powder: mp 126−127 °C; $[\alpha]^{25}_D$ +39.8° (*c* 2.1, $CHCl_3$); ^{1}H NMR δ 11.5−11.1 (br s, 1H), 7.40−7.10 (m, 10H), 6.80 (d, 1H, *J* = 5), 5.49 (d, 1H, *J* = 4), 5.07 (s, 2H), 4.49−4.46 (m, 1H), 4.25−4.23 (m, 1H), 3.18 (dd, 1H, *J* = 14, 5.5), 3.03 (dd, 1H, *J* = 14, 6.5), 1.28 (d, 3H, *J* = 7). Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 64.8; H, 6.0; N, 7.6. Found: C, 64.8; H, 6.0; N, 7.4.

BOC-Ile-Phe-OMe (26). BOC-isoleucine (**25**, 0.5 g, 2.2 mmol), Phe-OMe·HCl, (0.464 g, 100 mol %), and HOBT (0.29 g, 100 mol %) were dissolved in 5 mL of dry THF to which **1** was added (0.58 g, 100 mol %) followed by 0.24 mL (100 mol %) of *N*-methylmorpholine. The reaction mixture was stirred at rt for 16 h, and then isolation followed the general procedure. The resulting solid was recrystallized from THF/hexane to give **26**, 0.709 g, 82%. An identical reaction run in DMF gave **26** in 84% yield: mp 113−114 °C; $[\alpha]^{25}_D$ −27° (*c* 1.2, EtOH); ^{1}H NMR δ 7.30−7.11 (m, 5H), 6.31 (d, 1H, *J* = 6.8), 5.00 (d, 1H, *J* = 8.2), 4.90−4.84 (m, 1H), 3.95−3.90 (m, 1H), 3.71 (s, 3H), 3.11 (t, 2H, *J* = 5.3), 1.88−1.80 (m, 1H). 1.44 (s, 9H), 0.88 (d, 3H, *J* = 6.8). Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.3; H, 8.2; N, 7.1. Found: C, 64.6; H, 8.3; N, 7.0.

L,L-CBZ-Ala-Phe-Gly-OBn (27). Dipeptide **11** (0.2 g, 0.54 mmol), Gly-OBn·TsOH (0.364 g, 200 mol %), and HOBT (88 mg, 120 mol %) were combined in 4 mL of dry DMF. *N*-Methylmorpholine was added (0.18 mL, 300 mol %) followed by the addition of 0.16 g (110 mol %) of **1**. The reaction mixture was allowed to stir for 4 h at rt, after which isolation followed the general procedure. The white solid residue obtained from evaporation of the organic extracts was completely dissolved into ethyl acetate, and the resulting was analyzed by normal phase HPLC (eluting with ethyl acetate/hexane, 1/1, at 1 mL/min), which indicated 0.68% of the L,D diastereomer of **27**. Combined yield of products was 81%. In another experiment, a similar reaction was allowed to stir for 20 h, giving 1.3% of the L,D diastereomer as determined by HPLC. Combined yield of products was 90%. Recrystallization of the product mixture (THF/hexanes) gave pure L,L-**27** as a white solid: mp 160−163 °C; $[\alpha]^{25}_D$ −43.1° (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.48−7.21 (m, 15H), 6.65−6.58 (m, 2H), 5.27 (d, 1H, *J* = 6.6), 5.13 (s, 2H), 5.08 (d, 1H, *J* = 12), 5.00 (d, 1H, *J* = 12), 4.74 (dd, 1H, *J* = 7.2, 15), 4.16 (t, 1H, *J* = 6.7), 4.13−3.87 (m, 2H), 3.20−3.00 (m, 2H), 1.23 (d, 3H, *J* = 7). Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 67.3; H, 6.0; N, 8.1. Found: C, 66.9; H, 6.0; N, 8.1.

Synthesis of 27 in the Presence of $CuCl_2$. Dipeptide **11** (0.2 g, 0.54 mmol), Gly-OBn·TsOH (0.364 g, 200 mol %), and HOBT (88 mg, 120 mol %) were combined in 4 mL of dry DMF. *N*-Methylmorpholine was added (0.18 mL, 300 mol %) followed by the addition of 0.16 g (110 mol %) of **1** and 90 mg of anhydrous $CuCl_2$ (50 mol %). The reaction mixture was allowed to stir for 4 h at rt, after which isolation followed the general procedure. The white solid obtained from the organic extracts was completely dissolved into ethyl acetate, and the resulting solution was analyzed by HPLC, which indicated <0.1% of the L,D diastereomer of **27**. Combined yield of products was 71%. In another experiment, a similar reaction was allowed to stir for 20 h. This reaction gave <0.1% of the L,D diastereomer as determined by HPLC. Combined yield of products was 78%. Recrystallization of the product mixture gave pure **27**, identical to **27** prepared above.

Benzyl Crotonate. Benzyl 3-hydroxybutanoate[16] (0.46 g, 2.4 mmol), CuCl (11 mg, 5 mol %), and **1** (0.7 g, 110 mol %) were combined in 20 mL of dry CH_3CN and heated to 60 °C for 16 h. The reaction mixture was cooled and evaporated, followed by isolation according to the general procedure to give benzyl crotonate (0.346 g, 83%) as a mobile oil: IR 3060, 3030, 1720; ^{1}H NMR δ 7.40−7.20 (m, 5H), 7.00 (dq, 1H, *J* = 15.5, 6.9), 5.86 (dq, 1H, *J* = 16.0, 1.6), 5.18 (s, 2H), 1.83 (dd, 3H, *J* = 1.7, 6.9).

(16) Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 2952.