Synthesis of Hydroxamic Esters via Alkoxyaminocarbonylation of β-Dicarbonyl Compounds

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N-*t*-Butoxycarbonyl-*O*-sulfonyl-substituted hydroxylamines react with soft enolates to yield *O*-*t*-butoxycarbonylamino derivatives rather than the expected Boc-protected amino acids. The reaction is limited to enolates of β-dicarbonyl compounds. Decarboxylation of the resultant tricarbonyl compound affords malonyl α-alkyl *O*-*t*-butoxycarbonylamino derivatives.

Introduction

Hydroxamic acids have long been associated with diverse biological activities including antiinflammatory, antibacterial, antifungal, and antitumor profiles that are becoming increasingly important in medicinal chemistry.[1] As shown by elegant X-ray crystallographic studies,[2] these compounds are known to inhibit matrix metalloproteases (MMPs), a class of enzymes implicated in several diseases, by virtue of their ability to form a bidentate chelate with an active site zinc atom.[3] The more potent inhibitors for some MMPs, such as thermolysin, collagenase, elastase, neutral endopeptidase, and endothelin converting enzyme, are hydroxamic acid analogues of malonic esters.[4]

Hydroxamic acids are usually prepared by reacting hydroxylamine with an activated carboxylic derivative.[5] In a number of cases, side reactions such as nitrogen and oxygen acylations decrease the yields and make purification difficult.[6] Moreover, aliphatic acid chlorides are known to decompose in the presence of hydroxylamine, which is also prone to be explosive under certain conditions making scale-up operations hazardous. To circumvent these problems, many substituted hydroxylamine derivatives have been prepared, but they can be difficult to handle, deprotect, and prepare.[7]

Scheme 1

Previous publications from this laboratory have shown that 2-alkylpyridyl sulfonates are excellent leaving groups that can be displaced by halide ion even at 0 °C to give the corresponding alkyl halide. These reagents were based on a design element that capitalized on internal activation (Scheme 1). The enhanced reactivity of this leaving group was attributed[8] to a pre-coordination of a divalent metal salt to the pyridyl nitrogen, thus promoting nucleophilic displacement with release of an intramolecularly coordinated 2-pyridylsulfonate. The analogous reactions with *p*-tolylsulfonates were more sluggish.

Based on the same notion, we anticipated that *N*-butoxycarbonyl(2-pyridylsulfonyl)hydroxylamine **(1a)** would act as an electrophilic NHBoc transfer agent when reacted with enolates (Scheme 2). Electrophilic aminations with "activated amines" are well-known, although successful applications have been limited.[9] Activation has been achieved through the use of suitable leaving groups. For example, reagents of the type *p*-MeC_6H_6-$SO_2ONHBoc$ have been shown to transfer NHBoc to carbanions, albeit in modest yields.[10] It is interesting to point out that it is

(1) (a) Onishi, H. R.; Pelak, B. A.; Gerckens, L. S.; Lilver, L. L.; Fredrick, M. K.; Chen, M.; Patchet, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. H. *Science* **1996**, *274*, 980−982. (b) Gearing, A. J. H.; Beckett, P.; Christodoulou, M.; Churchill, M.; Clements, J.; Davidson, A. H.; Drummond, A. H.; Galloway, W. A.; Gilbert, R.; Gordon, J. L.; Leber, T. M.; Mangan, M.; Miller, K.; Nayee, P.; Owen, K.; Patel, S.; Thomas, W.; Wells, G.; Wood, L. M.; Woolley, K. *Nature* **1994**, *370*, 555−557. (c) Patel, D. V.; Young, M. G.; Robinson, S. P.; Hunihan, L.; Dean, B. J.; Gordon, E. M. *J. Med. Chem.* **1996**, *39*, 4197−4210. (d) Kleinman, E. F.; Campbell, E.; Giordano, L. A.; Cohan, V. L.; Jenkinson, T. H.; Cheng, J. B.; Shirley, J. T.; Pettipher, E. R.; Salter, E. D.; Hibbs, T. A.; DiCapua, F. M.; Bordner, J. *J. Med. Chem.* **1998**, *41*, 266−270. (e) Powers, J. C.; Harper, J. W. In *Proteinase Inhibitors*; Barret, A. J., Salvesen, G., Eds.; Elsevier: Amsterdam, 1986; pp 244−298.

(2) Holmes, M. A.; Matthews, B. W. *Biochemistry* **1981**, *20*, 6912−6920.

(3) (a) Levy, D. E.; Lapierre, F.; Liang, W.; Ye, W.; Lange, C. W.; Li, X.; Grobelny, D.; Casabonne, M.; Tyrrel, D.; Holme, K.; Nadzan, A.; Galardy, R. E. *J. Med. Chem.* **1998**, *41*, 199−223. (b) MacPherson, L. H.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R.; Justice, M. R.; Zhu, L.; Hu, S.; Melton, R. A.; Fryer, L.; Goldberg, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V.; Parker, D. T. *J. Med. Chem.* **1997**, *40*, 2525−253.

(4) (a) Bihovsky, R.; Levinson, B. L.; Loewi, R. C.; Erhardt, P. W.; Polokoff, M. A. *J. Med. Chem.* **1995**, *38*, 2119−2129. (b) von Roedern, E. G.; Grams, F.; Brandstetter, H.; Moroder, L. *J. Med. Chem.* **1998**, *41*, 339−345. (c) Nishino, N.; Powers, J. C. *Biochemistry* **1978**, *17*, 2846−2850. (d) Chérot, P.; Devin, J.; Fournié-Zaluski, M. C.; Roques, B. P. *Mol. Pharm.* **1986**, *30*, 338−344.

(5) For reviews, see: (a) Sandler, S. R.; Karo, W. In *Organic Functional Group Preparations*; Wasserman, H. H., Ed.; Academic Press: San Diego, 1989; Vol. 3, pp 482−522. (b) Bauer, L.; Exner, O.; *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376−384.

(6) Side reactions include diacylation on nitrogen, nitrogen, and oxygen acylation and triacylation. See, for example, ref 5a,b as well as: Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284−294.

(7) Romine, J. *Org. Prep. Proc. Int.* **1996**, 251−288.

(8) Hanessian, S.; Kagotani, M.; Komaglou, K. *Heterocycles* **1989**, *28*, 2, 1115−1120.

(9) For reviews, see: Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947−1980. Greck, C. G.; Genet, J. P. *Synlett* **1997**, 741−748. Mulzer, J.; Altenbach, H. J.; Braun, M.; Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights*; VCH Publishers: Weinheim, 1991; pp 45−53.

(10) (a) Genet, J. P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359−2362. (b) Zheng, N.; Armstrong, J. D.; McWilliams, C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817−2820.

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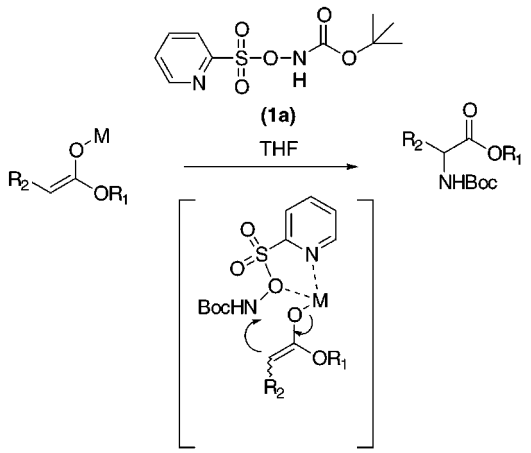
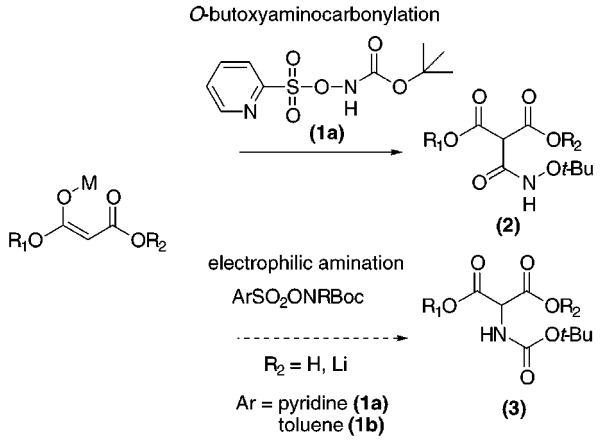
Scheme 2



Scheme 3



the N-lithiated form[11] of the reagent that is actually the electrophilic species in these reactions.

Results and Discussion

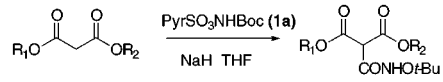
Based on the above precedents and our expectations of internal assistance in S_N2-displacement reactions,[8] we studied the reaction of the sulfonyl hydroxylamine derivative **1a** with ester enolates such as malonates and alkyl carboxylates. To our surprise, reaction took place to give *O*-*t*-butoxycarbonylamino derivatives **2**, rather than the expected NH-Boc α-amino acids **3** (Scheme 3).

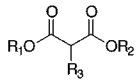
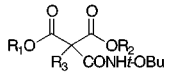
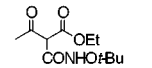
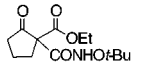
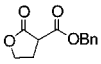
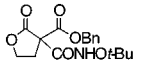
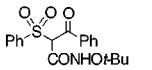
Initially, we were misled into assuming that we had indeed achieved electrophilic aminations with "designed" reagents such as **1a**, since the expected products were isomeric with the hydroxamates (Scheme 3). Mass spectral and NMR analyses were not immediately conclusive. An X-ray crystal structure of compound **2** ($R_1 = R_2 = Me$) revealed in fact the incorporation of the *O*-*t*-butoxycarbonylamino motif in the malonate.

A variety of ester and amide enolates (Ti, Cu, Li, Na, K, Zn, Mg, and Ce) of alkyl carboxylic acids as well as silyl enol ethers and enamines were found not to react with reagent **1a** or **1b** and led to the recovery of the respective carbonyl compounds. The only exception was the successful O-butoxyaminocarbonylation of the Zn enolate of phenyl acetic acid isopropyl ester with **1b**.

(11) (a) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016−6023. (b) Boche, G.; Wagner, H. U. *J. Chem. Soc., Chem. Commun.* **1985**, 1591−1592. (c) Armstrong, D. R.; Snaith, R.; Walker, G. T. *J. Chem. Soc., Chem. Commun.* **1984**, 789−791.

Table 1. *O*-Butoxyaminocarbonylation of Enolates



Substrate	Product	Yield[a]
		
	(5) $R_1 = R_2 = Me$, $R_3 = H$	76%
	(6) $R_1 = R_2 = Et$, $R_3 = Me$	51%
	(7) $R_1 = R_2 = R_3 = Et$	64%[b]
	(8) $R_1 = R_2 = Et$, $R_3 = Bn$	42%
	(9) $R_1 = Me$, $R_2 = Bn$, $R_3 = H$	48%
	(10) $R_1 = Me$, $R_2 = Bn$, $R_3 = Me$	55%
	(11) $R_1 = Et$, $R_2 = Allyl$, $R_3 = H$	48%
	(12) $R_1 = Me$, $R_2 = Allyl$, $R_3 = H$	60%
	(13) $R_1 = t\text{-}Bu$, $R_2 = Allyl$, $R_3 = Me$	44%
	**(14)** 	71%
	**(15)** 	67%
	**(16)** 	43%
	**(17)** 	32%

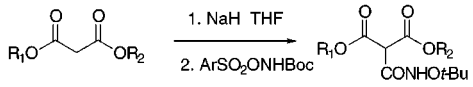
[a] Yield of isolated pure product, [b] LiBr (4 equiv) was added to enolate; in the absence of LiBr, the yield was 35%.

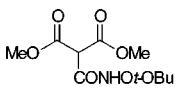
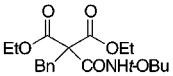
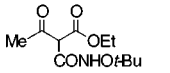
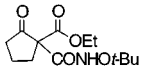
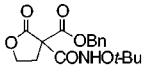
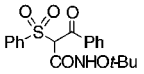
However, enolates of dicarbonyl compounds or those substituted with an electron-withdrawing group afforded the corresponding *O*-*t*-butoxycarbonylamino analogues in good to moderate yields (Scheme 3). Thus, malonates, 2-substituted malonates, acyclic and cyclic β-keto esters, α-alkoxy carbonyl lactones, and β-keto sulfones proved to be good substrates for this reaction as seen in Table 1. Yields for the unsubstituted and substituted malonates varied with the nature of the ester and α-substituents.

The *O*-*t*-butoxyaminocarbonylation of β-dicarbonyl ester enolates was optimized by a systematic study of the nature of the hydroxylamine reagent. The 2-pyridylsulfonyl reagent **1a** and the tosyl reagent **1b**[10a] are crystalline solids that can be stored at 0 °C for many months without decomposition. In general, the 2-pyridylsulfonyl reagent **1a** gave higher yields than the tosyl reagent **1b** (Table 2) and was consistently more efficient than the nosyl and mesyl derivatives. Unlike the tosyl reagent **1b**, unreacted 2-pyridyl reagent **1a** unfortunately cannot be recovered after the reaction. Reagents with a Cbz group in place of a Boc group and reagents where the *O*-arylsulfonyl portion of the molecule was replaced by a 2-mercaptopyridine or a OTBDMS group were unreactive. Replacement of the sulfonyl group with a carbonyl or phosphoryl group resulted in reagents that were unreactive. The *O*-*t*-butoxyaminocarbonylation reaction was more efficient when the protonated form of **1a** or **1b** was added to the reaction containing an excess of base rather than adding the preformed metalated reagent (Li, Na, Mg, Cu, or Zn salts), which is unstable even at 0 °C.

In the cases of less reactive β-dicarbonyl enolates (Table 1), the modest yields could be attributed to protonation of the enolate by the acidic reagent. With the deuterated reagent, $PyrSO_2ONDBoc$, deuterium transfer

Table 2. Comparison of Tolyl and Pyridyl Reagents



Product	TsONHBoc (**1b**) [a]	$PyrSO_2ONHBoc$ (**1a**) [a]
	66% (77%)[b]	90% (82%)[b]
	44%	42% (0%)[d]
	75%	92%
	70% (0%)[c]	66% (46%)[d]
	43%	48% (43%)[d]
	54%	32%

[a] Percent conversion to product with Na enolate unless noted otherwise, [b] Percent conversion to product with Li enolate, [c] With the deprotonated tosyl reagent, no reaction occurred. [d] With 4−6 equiv of LiBr added to reaction.

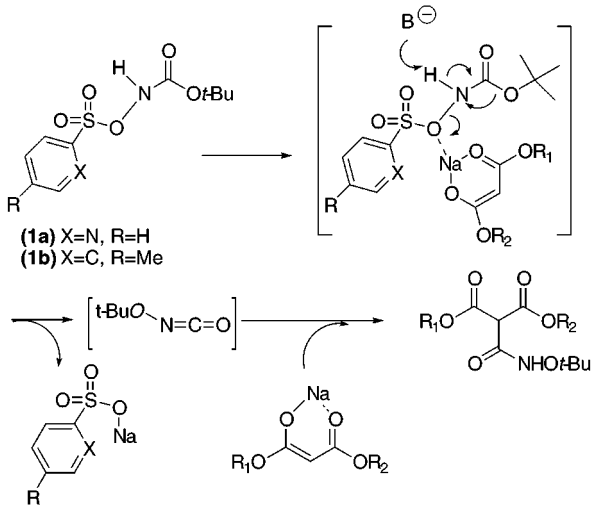
was observed in reactions with diethyl malonate. No reaction took place with the *N*-methyl analogue of the reagent.

The nature of the solvent and additives such as lithium chloride or lithium bromide were found to have significant effects on the yields. THF, diethyl ether, ether/hexanes, benzene, and toluene[12] were found to be suitable solvents. Polar solvents, such as HMPA, DME, TMEDA, and MeOH, which are known to promote cation dissociation and increase nucleophilicity,[13] impede the reaction. Dichloromethane was not a suitable solvent.

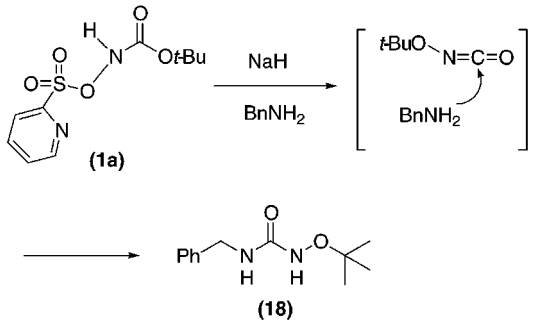
Addition of lithium bromide to the reactions of sodium diethyl malonate and reagent **1a** was found to increase the yield substantially.[14] Surprisingly, yields of other reactions in the presence of LiBr were diminished by as much as 20%, and the reaction failed altogether with diethyl benzyl malonate. These changes in reactivity may be due to a change in enolate geometry, solvent polarity, or aggregation state, which LiBr is known to cause,[13] or from a change in the counterion of the enolate. In fact, lithium and potassium enolates were also found to be less reactive than sodium enolates (Table 2). Changes in the bulk of the ester moiety, which can also affect enolate geometry, led to a decrease in yield (Table 1).

A Lossen-type rearrangement is a likely mechanistic rational for the *O*-*t*-butoxyaminocarbonylation reaction, since such rearrangements with *O*-sulfonyl-substituted hydroxamic acids have been observed before.[15] Boche and co-workers have studied the Li salt of the tosyl reagent **1b** by X-ray crystallography and found that the C−O−

Scheme 4



Scheme 5



tert-butyl bond is lengthened by 5 pm relative to the neutral reagent.[16] A similar bond lengthening has been observed with lithium enolates, and elimination of LiOR to form ketenes has been postulated.[17] A plausible mechanism to explain the unprecedented formation of the tricarbonyl hydroxamates of the type reported here is shown in Scheme 4.

Base-induced deprotonation and concomitant migration of the *O*-*t*-butoxy group with departure of the arylsulfonyloxy group generates a *O*-*t*-butoxy isocyanate intermediate, which acylates the enolate. Although some examples of alkoxy isocyanates are known, they are reported to be unstable.[18] When the reaction was done with an ethoxycarbamate reagent, the product was the corresponding *N*-ethoxy derivative of **2**. As expected from the postulated mechanism, no reaction occurred with the *N*-methyl reagent. To give credence to the isocyanate mechanism, we treated the reagent **1a** with NaH and benzylamine. Only the urea derivative **18** was found rather than the hydrazide (Scheme 5). When the original reaction was done in the presence of benzylamine and sodium dimethyl malonate, the major product was the urea resulting from the acylation of the more basic nucleophile.

The differences in reactivities between **1a** and **1b** are possibly due to the better coordinating ability of **1a**, thus

(12) Insolublity problems with toluene lowered the yields.

(13) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737−2769.

(14) Lithium halides are known to increase the yields of enolate reactions. See, for example: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

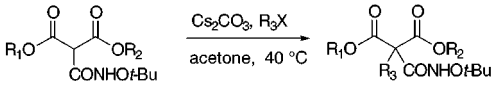
(15) Pihuleac J.; Bauer, L. *Synthesis* **1989**, 61−64.

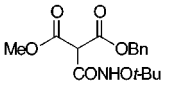
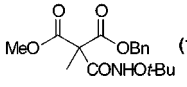
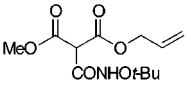
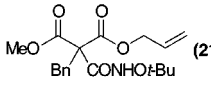
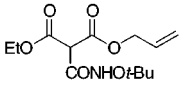
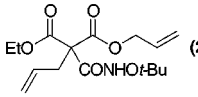
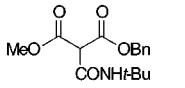
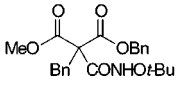
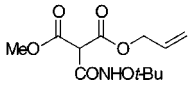
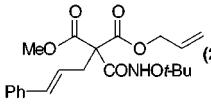
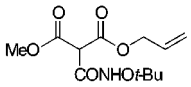
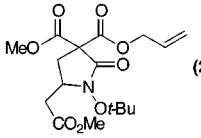
(16) Boche, G.; Boie, C.; Bosold, F.; Harms, K.; Marsch, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 115−117.

(17) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403−5409.

(18) (a) Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. RR. *Synthesis* **1994**, 846−850. (b) Sheludyakov, V. D.; Gusev, A. I.; Dmitrieva, A. B.; Los', M. G.; Kirilin, A. D. *Zh. Obshch. Khim.* **1984**, *53*, 2051−2054. (c) Maier, G.; Teles, J. H. *Chem. Ber.* **1989**, *122*, 745−748. (d) Mormann, W.; Leukel, G. *Synthesis* **1988**, 990−991.

Table 3. Alkylation of *O*-*t*-Butoxycarbonylamino Malonates



Substrate	Product		Yield[a]
		**(10)**	50%[b,c]
		**(21)**	72%[d]
		**(20)**	76%[b]
		**(19)**	52%[d,e]
		**(22)**	42%[d]
		**(23)**	74%[d]

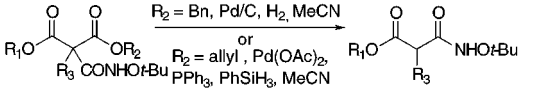
[a] Yield of isolated pure product. [b] Alkylated with alkyl iodide. [c] With K_2CO_3, yields ranged from 24 to 37%. [d] Alkylated with alkyl bromide, [e] K_2CO_3 was used as a base.

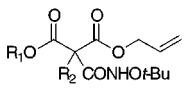
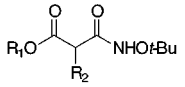
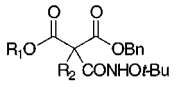
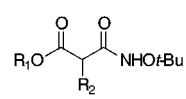
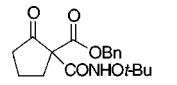
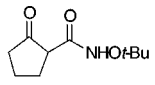
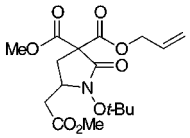
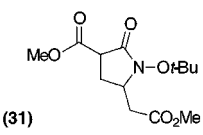
enhancing the leaving group character of the 2-pyridylsulfonyloxy group compared to the tosyloxy group. As previously mentioned, it is also of interest to note that the reactions were less efficient when the preformed lithium salts of **1a** and **1b** were used instead of the neutral reagents.

Having demonstrated the viability of generating alkyl malonic acid *O*-*t*-butoxycarbonylamino derivatives from substituted enolates, we turned our attention to an alternate method where the malonic acid is first converted to the *O*-*t*-butoxycarbonylamino derivative and then alkylated. Decarboxylation of these tricarbonyl compounds would afford the corresponding malonyl *O*-*t*-butoxycarbonylamino derivatives. Alkylations of hydroxamic acids are well-known to produce unpredictable mixtures of compounds due to multiple nucleophilic sites.[6] Since our substrates have an acidic proton on the central malonyl carbon atom, alkylation was potentially even more problematic.[19] However, treatment of the tricarbonyl substrate with 1 equiv of Cs_2CO_3 and alkyl halides led to the desired α-alkylated derivatives (Table 3). Mixtures of N- and C-alkylated products were obtained in the case of dicarbonyl substrates with excess Cs_2CO_3 or with other bases (NaH, KH, *t*-BuOK, etc.).

These products were easily transformed in one step to the corresponding malonic ester *O*-*t*-butoxycarbonyl-

Table 4. Pd-Catalyzed Decarboxylation of *O*-*t*-Butoxycarbonylamino Malonates



Substrate	Product	Yield[a]
		
	(24) R_1 = *t*-Bu, R_2 = Me	98%
	(25) R_1 = Et, R_2 = allyl	97%
	(26) R_1 = Me, R_2 = Bn	98%
	(27) R_1 = Me, R_2 = cinnamyl	84%
		
	(28) R_1 = Me, R_2 = H	93%
	(29) R_1 = Me, R_2 = Me	98%
	(26) R_1 = Me, R_2 = Bn	98%
		61%
	(30)	
		67%
	(31)	

[a] Yield of isolated pure product.

amino derivatives either by hydrogenation/decarboxylation of the benzyl ester or by palladium-catalyzed cleavage/decarboxylation of the allyl ester under mild conditions (Table 4).[20]

To our surprise, the *O*-*t*-butoxycarbonylamino malonic acid derivatives were found to be difficult to cleave. For example, cleavage of *O*-*t*-butoxycarbonylamino compounds has been reported to occur with hydrogen bromide only at elevated temperatures.[21] Our substrates were inert to acidic and S_N2-type conditions and underwent decomposition and decarboxylation at elevated temperatures. After several acids and conditions (anhyd HBr in AcOH, aqueous HBr, HCl in dioxane, aqueous HCl, H_2SO_4 in dioxane, bromocatecholborane, $B(OCOCF_3)_3$, BCl_3, $TiCl_4$, and TMS−I with and without *tert*-butyl scavengers) were screened, it was found that dichloromethane solutions of trifluoroacetic acid from freshly opened bottles were effective to cleave the O-*tert*-butyl group without decarboxylation (Figure 1). Older batches of TFA or TFA that was distilled over P_2O_5 were not effective.[22] Freshly opened bottles of TFA maintained under a N_2 atmosphere could be used for a period of 1 week before reactions became sluggish.

Conclusions

Hydroxamic acids of vicinal tricarbonyl compounds can be prepared in one step from *N*-sulfonylhydroxylamine

(19) Alkylation with 1 equiv of alkylating reagent and a variety of lithium, sodium, and potassium bases as well as Cs_2CO_3 or K_2CO_3 resulted in either no reaction, dialkylation on carbon, monoalkylation on nitrogen, or mixtures of carbon and nitrogen alkylation. Knoevenegal strategies were also unsuccessful.

(20) For decarboxylation of a β-keto ester substrate, see: Aboulhoda, S. J.; Henin, F.; Muzart, J.; Thorey, C. *Tetrahedron: Asymmetry* **1994**, *5*, 1321−1326. Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140−145.

(21) Kolasa, T.; Chimiak, A. *Tetrahedron* **1974**, *30*, 3591−3595.

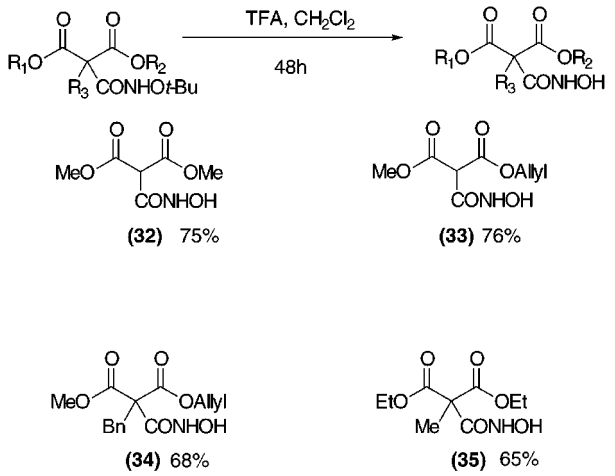


Figure 1. Deprotection of *O*-*t*-butoxycarbonylamino malonates.

reagents. Normally, to synthesize such compounds requires a three- or four-step sequence consisting of carboxylation of the enolate, activation of the carboxylate, reaction with hydroxylamine, and finally protection of the *N*-hydroxyl group. The pyridylsulfonyloxy reagent **1a**, in some cases, proved to be the most efficient reagent examined compared to the *N*-tosyl reagent **1b**. A series of α-alkyl tricarbonyl and α-alkyl dicarbonyl *O*-*tert*-butoxycarbonylamino derivatives were prepared, and a new cleavage of *O*-*tert*-butoxycarbonylamino malonates in this series was discovered. The products are closely related to well-known hydroxamic acid derivatives of malonates, which are inhibitors of MMPs. Previous syntheses of these compounds by other methods were complicated by side reactions, such as hydroxylamine reacting with the coupling reagent and N−O bond cleavage during deprotection.[4a] These problems are completely avoided with the 2-pyridylsulfonyloxy reagent.

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C spectra were recorded at 300 and 400 MHz in $CDCl_3$. IR spectra were recorded as KBr pellets or neat. Mass spectra were obtained at low and high resolution. Organic solvents were dried by standard methods. All reactions were monitored by TLC with Merck 60 F_{254} silica gel coated plates. Flash chromatography was carried out using 230−400 mesh silica gel under pressure. *N*-*tert*-Butoxycarbonylhydroxylamine was purchased from Lancaster and used without further purification and made by reported procedures.[23]

2-Pyridylsulfonyl Chloride. 2-Mercaptopyridine (20 g, 0.18 mol) was dissolved in concentrated HCl (160 mL), and chlorine gas was bubbled through at 0 °C for 2 h. The mixture was poured into ice−water (500 mL) and extracted three times with dichloromethane. The combined organic fractions were washed with brine and dried with Na_2SO_4. After filtering, concentration under reduced pressure yielded a clear oil that solidified to a white solid in the freezer. The reagent was pure and could be used directly in the syntheses of the hydroxamating reagents.

General Procedure for Synthesis of Hydroxamating Reagents. *N*-(*tert*-Butoxycarbonyl)-*O*-(2-pyridinylsulfonyl)hydroxylamine (1). 2-Pyridylsulfonyl chloride (3.529 g,19.87 mmol) and Et_3N (2.011 g, 19.87 mmol) were dissolved in benzene (140 mL) and cooled to 0 °C. After 10 min, *N*-*tert*-butoxylcarbonyl hydroxylamine (2.646 g, 19.87 mmol) was added as a solution in benzene (50 mL). The mixture stirred for 30 min at 0 °C and was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted three times with Et_2O, and the combined organic fractions were washed with brine and dried with Na_2SO_4. The mixture was filtered, concentrated, and purified by recrystallization in EtOAc and hexanes or by flash chromatography on silica gel (hexanes/EtOAc 9:1, 2:1) to yield **1a** as a white solid (3.2293 g, 11.73 mmol, 59%): R_f = 0.37 on silica gel (2:1 hexanes/ethyl acetate); mp 58−59 °C; IR (KBr pellet) 3450, 3140, 3020, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79−8.77 (m, 1H), 8.12−8.09 (m, 1H), 8.00−7.96 (m, 1H), 7.84 (s, 1H), 7.63−7.59 (m, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.3, 152.5, 150.3, 138.2, 128.2, 124.9, 83.9, 27.7; HRMS calcd for $C_{10}H_{15}N_2SO_6$ 275.0701, found 275.0707. Anal. Calcd for $C_{10}H_{14}N_2SO_6$: C, 43.7; H, 5.1; N, 10.2; S, 11.6. Found: C. 43.9; H, 5.1; N, 10.2; S, 11.6.

General Procedure for *N*-*t*-Butoxycarbonylamination of Enolates. NaH (60% dispersion in mineral oil, 1.5−2 equiv) was weighed into a dry round-bottom flask equipped with a stirring bar and capped with a rubber septum, and dry THF was added. The slurry was adjusted to the required temperature, and the malonate substrate (1 equiv) in dry THF was transferred with a cannula to the slurry. The mixture stirred for 10−60 min, and the O-*t*-butoxyaminocarbonylation reagent (1 equiv) was added with a cannula as a solution in THF dropwise over 20 min. The mixture was stirred at reduced temperature and warmed to room temperature. After being stirred for several h, the reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted four times with EtOAc, and the combined organic phases were washed with brine and dried with Na_2SO_4. The solution was filtered, and the filtrate was concentrated under reduced pressure. The product was purified by flash chromatography on silica gel eluting with mixtures of hexanes and ethyl acetate.

2-*tert*-Butoxycarbamoylmalonic Acid Dimethyl Ester (5). According to the general procedure, dimethyl malonate (57.8 mg, 0.437 mmol) was acylated with NaH (11 mg, 0.454 mmol) and **1a** (125 mg, 0.454 mmol) in THF (4 mL) at − 78 °C (1 h) and then at room temperature (1.5 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1, 2:1, yielded **5** (81.3 mg, 0.33 mmol, 76%) as a white solid: R_f = 0.53 on silica gel (2:1 hexanes/ethyl acetate); mp 88−90 °C; IR (neat) 3222, 1759, 1675, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 4.42 (s, 1H), 3.82 (s, 6H), 1.29 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 160.4, 83.1, 58.1, 53.5, 26.1; HRMS calcd for $C_{10}H_{18}NO_6$ 248.1126, found 248.1134.

2-*tert*-Butoxycarbamoyl-2-methylmalonic Acid Diethyl Ester (6). According to the general procedure, diethyl ethylmalonate (38 mg, 0.218 mmol) was acylated with NaH (8 mg, 0.33 mmol) and **1a** (60 mg, 0.218 mmol) in THF (4 mL) at − 40 °C (1 h) and then at room temperature (1.5 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1−2:1, yielded **6** (32.3 mg, 0.11 mmol, 51%): R_f = 0.45 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3438, 1756 (br), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 4.22 (q, 1H, J = 9.3, 2.2 Hz), 1.65 (s, 3H,)1.26 (t, 6H, J = 10.1, 7.1 Hz), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.3, 82.9, 72.5, 62.9, 27.3, 16.8, 13.9; HRMS calcd for $C_{13}H_{24}NO_6$ 290.1603, found 290.1595.

2-*tert*-Butoxycarbamoyl-2-ethylmalonic Acid Diethyl Ester (7). According to the general procedure, diethyl ethyl malonate (41 mg, 0.218 mmol) was acylated with NaH (13 mg, 0.33 mmol), LiBr (76 mg, 0.872 mmol), and **1a** (60 mg, 0.218 mmol) in THF (4 mL) at −40 °C (3 h) and then at room temperature (3 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 5:1, yielded **7** (42 mg, 0.138 mmol, 64%): R_f = 0.72 on silica gel (1:1 hexanes/ethyl acetate); IR (neat) 3310, 1760, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 4.20 (q, 4H, J = 7.2, 6.5 Hz), 2.56 (q, 2H, J = 14.7, 7.7 Hz), 1.27 (s, 9H), 1.22 (t, 6H, J = 13.6, 6.5 Hz), 0.87

(22) We thank one of the reviewers for suggesting the use of triethylsilane in conjunction with TFA. This appeared to give less colored solutions, but the yields were not improved.

(23) Baldwin, J. E.; Adlington, R. M.; Mellor, L. C. *Tetrahedron* **1994**, *50*, 5049−5066.

(24) Falik, Z.; Plazek, E. *Acta Pol. Pharm.* **1955**, *12*, 5.

(t, 3H, J = 15.1, 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 164.6, 82.6, 65.5, 62.3, 27.6, 26.3, 13.9, 9.0; HRMS calcd for $C_{14}H_{26}NO_6$ 304.1749, found 304.1760.

2-*tert*-Butoxycarbamoyl-2-benzylmalonic Acid Diethyl Ester (8). According to the general procedure, diethyl benzyl malonate (55 mg, 0.219 mmol) was acylated with NaH (8 mg, 0.33 mmol) and **1a** (60 mg, 0.219 mmol) in THF (4 mL) at 0 °C (45 min) and then at room temperature (3 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 6:1, yielded **8** (33.3 mg, 0.091 mmol, 42%): R_f = 0.58 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3940, 3327, 1761, 1729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.27−7.20 (m, 3H), 7.12−7.05 (m, 2H), 4.25 (q, 4H, J = 7.1, 1.54 Hz), 3.63 (s, 1H), 1.28 (t, 6H, J = 14.3, 7.1 Hz), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 163.8, 134.8, 129.6, 128.5, 127.4, 82.7, 62.5, 39.7, 28.0, 26.1, 13.9; HRMS calcd for $C_{19}H_{28}NO_6$ 366.1905, found 366.1916.

2-*tert*-Butoxycarbamoylmalonic Acid Benzyl Ester Methyl Ester (9). According to the general procedure, benzyl methyl malonate (189 mg, 0.911 mmol) was acylated with NaH (55 mg, 1.37 mmol) and **1a** (250 mg, 0.911 mmol) in THF (50 mL) at 0 °C (0.5 h) and then at room temperature (4 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 3:1, yielded **9** (140 mg, 0.433 mmol, 48%): R_f = 0.32 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3227, 1732 (br), 1682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.32 (m, 5H), 5.20 (s, 2H), 4.42 (s, 1H), 3.74 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.9, 160.4, 134.5, 128.6, 128.6, 128.4, 128.3, 83.0, 68.3, 50.3, 53.4, 26.1; HRMS calcd for $C_{16}H_{22}NO_6$ 324.1454, found 324.1447.

2-*tert*-Butoxycarbamoyl-2-methylmalonic Acid Benzyl Ester Methyl Ester (10). According to the general procedure, methyl benzyl methyl malonate (1 g, 0.446 mmol) was acylated with NaH (268 mg, 6.69 mmol) and **1a** (1.223 g, 4.46 mmol) in THF (150 mL) at 0 °C (1 h) and then at room temperature (1 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 9:1, yielded **10** (822.8 mg, 2.44 mmol, 55%). Alternatively, **10** was made according to the general procedure for alkylation of *O*-*t*-butoxycarbonylamino derivatives (see below) by mixing **9** (25 mg, 0.0773 mmol) with Cs_2CO_3 (23 mg, 0.0696 mmol) and iodomethane (13.2 mg, 0.0928 mmol) in acetone (5 mL) at 40 °C for 4 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 3:1, yielded **10** (13 mg, 0.039 mmol, 50%): R_f = 0.36 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3325, 1733, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.40−7.24 (m, 5H), 5.21 (d, 2H, J = 3.6 Hz), 3.71 (s, 3H), 1.77 (s, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.5, 165.2, 134.6, 128.5, 128.1, 126.8, 82.7, 68.0, 60.4, 53.2, 26.0, 20.3; HRMS calcd for $C_{17}H_{24}NO_6$ 338.1618, found 338.1603.

2-*tert*-Butoxycarbamoylmalonic Acid Allyl Ester Ethyl Ester (11). According to the general procedure, allyl ethyl malonate (336 mg, 1.95 mmol) was acylated with NaH (130 mg, 3.25 mmol) and **1a** (595 mg, 2.17 mmol) in THF (50 mL) at 0 °C (1 h) and then at room temperature (4 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 5:1 then 3:1, yielded **11** (269 mg, 0.936 mmol, 48%) as clear crystals: R_f = 0.36 on silica gel (2:1 hexanes/ethyl acetate); mp 39−41 °C; IR (neat) 3227, 1756, 1677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 5.90−5.75 (m, 1H), 5.32−5.15 (m, 2H), 4.62 (q, 2H, J = 5.9, 1.2 Hz), 4.37 (s, 1H), 4.18 (q, 2H, J = 9.4, 2.2 Hz), 1.22 (s, 9H), 1.22 (t, 3H, J = 5.1, 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 164.9, 160.6, 130.7, 119.4, 83.0, 67.1, 62.9, 58.4, 26.1, 13.9; HRMS calcd for $C_{13}H_{22}NO_6$ 288.1447, found 288.1440.

2-*tert*-Butoxycarbamoylmalonic Acid Allyl Ester Methyl Ester (12). According to the general procedure, allyl methyl malonate (620 mg, 0.392 mmol) was acylated with NaH (235 mg, 5.88 mmol) and **1a** (1.075 g, 3.92 mmol) in THF (120 mL) at 0 °C (1 h) and then at room temperature (3 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 3:1, yielded **12** (645 mg, 2.36 mmol, 60%): R_f = 0.15 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3213, 1760, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 5.95−5.80 (m, 1H), 5.38−5.23 (m, 2H), 4.67 (d, 2H, J = 5.8 Hz), 4.43 (s, 1H), 3.81 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 165.6, 164.8, 160.4, 130.6, 119.6, 83.1, 67.2, 58.4, 53.6, 26.2; HRMS calcd for $C_{12}H_{20}NO_6$ 274.1290, found 274.1295.

2-*tert*-Butoxycarbamoyl-2-methylmalonic Acid Allyl Ester *tert*-Butyl Ester (13). According to the general procedure, allyl *tert*-butyl methyl malonate (86 mg, 0.401 mmol) was acylated with NaH (24.1 mg, 6.69 mmol) and **1a** (1.223 g, 4.46 mmol) in THF (150 mL) at 0 °C (1 h) then at room temperature (1 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 9:1, yielded **13** (58.1 mg, 0.177 mmol, 44%): R_f = 0.32 on silica gel (4:1 hexanes/ethyl acetate); IR (neat) 3321, 1756, 1728 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 9.70 (s, 9H), 5.89−5.75 (m, 1H), 5.25 (dd, 1H, J = 17.2, 2.0 Hz), 5.17 (dd, 1H, J = 10.4, 1.3 Hz), 4.59 (d, 2H, J = 5.8 Hz), 1.63 (s, 3H), 1.37 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 167.8, 166.0, 131.0, 119.3, 83.7, 82.6, 66.8, 61.1, 27.7, 26.2, 20.6.

2-*tert*-Butoxycarbamoyl-3-oxobutyric Acid Ethyl Ester (14). According to the general procedure, ethyl acetoacetate (28.4 mg, 0.218 mmol) was acylated with NaH (7.9 mg, 0.33 mmol) and **1a** (60 mg, 0.218 mmol) in THF (4 mL) at −40 °C (2 h) and then at room temperature (3 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 3:1, yielded **14** (38 mg, 0.155 mmol, 71%): R_f = 0.64 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3390, 3000, 1800, 1740 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1H), 4.60 (s, 1H), 4.26 (dd, 2H, J = 14.3, 7.2 Hz), 2.45 (s, 3H), 1.36 (dd, 3H, J = 14.3, 7.1 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 171.4, 168.4, 93.7, 82.5, 60.8, 26.2, 25.9, 14.3; HRMS calcd for $C_{11}H_{20}NO_5$ 246.1341, found 246.1330.

1-*tert*-Butoxycarbamoyl-2-oxocyclopentanecarboxylic Acid Ethyl Ester (15). According to the general procedure, ethyl-2-oxocyclopentanecarboxylate (34 mg, 0.218 mmol) was acylated with NaH (13 mg, 0.33 mmol) and **1a** (60 mg, 0.218 mmol) in THF (4 mL) at −40 °C (1 h) and then at room temperature (4 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 3:1, yielded **15** (39 mg, 0.144 mmol, 66%) as a white solid: R_f = 0.27 on silica gel (2:1 hexanes/ethyl acetate); mp 57−59 °C; IR (neat) 3320, 1728 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 4.23 (q, 2H, J = 7.2, 3.2 Hz), 2.90−2.78 (m, 1H), 2.63−2.53 (m, 1H), 2.53−2.35 (m, 2H), 2.08−1.95 (m, 2H), 1.30−1.21 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 167.4, 162.7, 82.8, 67.3, 62.7, 38.4, 31.5, 26.1, 19.8, 13.9; HRMS calcd for $C_{13}H_{22}NO_5$ 272.1498, found 272.1504.

3-*tert*-Butoxycarbamoyl-2-oxotetrahydrofuran-3-carboxylic Acid Benzyl Ester (16). According to the general procedure, 2-oxotetrahydrofuran-3-carboxylic acid benzyl ester (40 mg, 0.182 mmol) was acylated with NaH (11 mg, 0.273 mmol) and **1a** (50 mg, 0.0.182 mmol) in THF (4 mL) at −40 °C (2 h) to −15 °C (2 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 2:1, yielded **16** (26 mg, 0.078 mmol, 43%): R_f = 0.29 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3329, 2928, 1767, 1744, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.38−7.30 (m, 5H), 5.24 (q, 2H, J = 12.1, 8.5 Hz), 4.45 (dd, 2H, J = 6.5, 5.4 Hz), 3.10−2.98 (m, 1H), 2.80 (m, 1H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 165.4, 161.1, 134.0, 129.0, 128.8, 128.5, 83.4, 69.1, 67.6, 60.8, 30.2, 26.0; HRMS calcd for $C_{17}H_{22}NO_6$ 336.1456, found 336.1447.

3-Benzenesulfonyl-*N*-*tert*-butoxy-3-oxo-3-phenylpropionamide (17). According to the general procedure, 2-(phenylsulfonyl)acetophenone (47.4 mg, 0.182 mmol) was acylated with NaH (11 mg, 0.273 mmol) and **1a** (50 mg, 0.182 mmol) in THF (4 mL) at 0 °C (0.5 h) and then at room temperature (3 h). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 2:1, yielded **17** (22 mg, 0.059 mmol, 32%): R_f = 0.14 on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3234, 1698, 1672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.85 (dd, 4H, J = 12.4, 7.3 Hz), 7.63−7.35 (m, 6H), 6.01 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 157.0, 137.3, 135.5, 134.9, 129.4, 129.2, 128.9, 83.8, 75.5, 26.2; HRMS calcd for $C_{19}H_{22}NSO_5$ 376.1218, found 376.1227.

***N*-Phenylmethyl-*N*′-*tert*-butoxyurea (18).** To a mixture of **1a** (66 mg, 0.24 mmol) and NaH (20 mg, 0.48 mmol) in 4 mL of THF was added benzylamine (26 mg, 0.24 mmol) at 0

°C (15 min) and then at room temperature (10 min). Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 2:1, yielded **18** (39 mg, 0.175 mmol, 73%) as clear crystals: $R_f = 0.44$ on silica gel (1:1 hexanes/ethyl acetate); mp 80−82 °C; IR (neat) 3439, 3205, 2931, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 6.82 (br s, 1H), 6.00 (br s, 1H), 4.48 (d, 2H, $J = 5.5$ Hz), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 138.6, 128.6, 127.4, 127.3, 80.8, 43.5, 26.3; HRMS calcd for $C_{12}H_{19}N_2O_2$ 223.1446, found 223.1453. The same result was obtained in the presence of dimethyl malonate.

General Procedure for Alkylation. Cs_2CO_3 or K_2CO_3 (0.9−0.95 equiv) was dried in an oven overnight and weighed into a dry round-bottom flask equipped with a stir bar and reflux condenser and capped with a rubber septum. Dry acetone was added, followed by the *O*-*t*-butoxycarbonylamino substrate (1 equiv). The mixture was stirred for 10 min, and the alkylating reagent (1.2−2.0 equiv) was added. After being heated at 40 °C for 2−17 h, the slurry was filtered and the filtrate was concentrated under reduced pressure. The product was purified on silica gel eluting with mixtures of hexanes and ethyl acetate.

2-*tert*-Butoxycarbamoyl-2-benzylmalonic Acid Benzyl Ester Methyl Ester (19). According to the general procedure, **9** (38 mg, 0.117 mmol) was alkylated with K_2CO_3 (15 mg, 0.106 mmol) and BnBr (24.3 mg, 0.142 mmol) in acetone (4 mL) at 40 °C for 3 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1, yielded **19** (27 mg, 0.065 mmol, 52%): $R_f = 0.49$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3330, 1765, 1732, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.46−7.34 (m, 4H), 7.23−7.21 (m, 4H), 7.10−7.02 (m, 2H), 5.29 (q, 2H, $J = 28.0, 12.0$ Hz), 3.75 (s, 3H), 3.70 (s, 2H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 167.5, 163.6, 134.6, 129.6, 128.7, 128.6, 128.5, 128.5, 127.5, 82.8, 68.1, 66.1, 53.2, 39.8, 26.1; HRMS calcd for $C_{23}H_{28}NO_6$ 414.1902, found 414.1916.

2-Allyl-2-*tert*-butoxycarbamoylmalonic Acid Allyl Ester Ethyl Ester (20). According to the general procedure, **11** (60 mg, 0.209 mmol) was alkylated with Cs_2CO_3 (61.2 mg, 0.188 mmol) and allyl iodide (42 mg, 0.251 mmol) in acetone (5 mL) at 40 °C for 6 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1, yielded **20** (52 mg, 0.159 mmol, 76%): $R_f = 0.64$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3328, 1762, 1731, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 5.90−5.75 (m, 1H), 5.75−5.55 (m, 1H), 5.38−5.09 (m, 4H), 4.64−4.61 (m, 2H), 4.23 (dd, 2H, $J = 14.3, 7.1$ Hz), 2.99 (dd, 2H, $J = 7.4, 0.9$ Hz), 1.26 (s, 9H), 1.25 (t, 3H, $J = 8.8, 5.5$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.6, 164.1, 131.2, 130.9, 120.1, 119.3, 82.8, 66.9, 64.6, 62.6, 38.6, 26.2, 13.9; HRMS calcd for $C_{16}H_{26}NO_6$ 328.1760, found 328.1771.

2-*tert*-Butoxycarbamoyl-2-benzylmalonic Acid Allyl Ester Methyl Ester (21). According to the general procedure, **12** (89 mg, 0.326 mmol) was alkylated with Cs_2CO_3 (101 mg, 0.31 mmol) and benzyl bromide (84 mg, 0.49 mmol) in acetone (3 mL) at 40 °C for 17 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1, yielded **21** (85 mg, 0.233 mmol, 72%): $R_f = 0.48$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3332, 1764, 1734, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.27−7.18 (m, 3H), 7.10−7.05 (m, 2H), 5.93−5.78 (m, 1H), 5.36−5.26 (m, 2H), 4.65 (dd, 2H, $J = 5.9, 1.4$ Hz), 3.78 (s, 3H), 3.64 (d, 2H, $J = 2.5$ Hz), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.4, 163.6, 134.6, 130.8, 129.6, 128.5, 127.5, 119.4, 82.8, 67.0, 66.0, 53.3, 39.8, 26.2; HRMS calcd for $C_{19}H_{26}NO_6$ 364.1760, found 364.1751.

2-*tert*-Butoxycarbamoyl-2-styrylmalonic Acid Allyl Ester Methyl Ester (22). According to the general procedure, **12** (40 mg, 0.146 mmol) was alkylated with Cs_2CO_3 (43 mg, 0.132 mmol) and cinnamyl bromide (35 mg, 0.175 mmol) in acetone (3 mL) at 40 °C for 7 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1, yielded **22** (24 mg, 0.062 mmol, 42%): $R_f = 0.52$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3329, 1762, 1762, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.29−7.18 (m, 5H), 6.43 (d, 2H, $J = 16.6$ Hz), 6.09−5.98 (m, 1H), 5.90−5.78 (m, 1H), 5.32−5.20 (m, 2H), 4.65−4.60 (m, 2H), 3.79 (s, 3H), 3.19 (d, 2H, $J = 6.6$ Hz), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 167.6, 164.1, 136.6, 134.9, 130.8, 128.5, 127.7, 123.3, 119.4, 82.9, 67.0, 64.9, 53.4, 38.0, 26.2; HRMS calcd for $C_{21}H_{28}NO_6$ 390.1916, found 390.1925.

1-*tert*-Butoxy-5-methoxycarbonylmethyl-2-oxo-pyrrolidine-3,3-dicarboxylic Acid Allyl Ester Methyl Ester (23). According to the general procedure, **12** (59 mg, 0.216 mmol) was alkylated with Cs_2CO_3 (67 mg, 0.205 mmol) and methyl-4-bromocrotonate (47 mg, 0.346 mmol) in acetone (5 mL) at 40 °C for 6 h. Flash chromatography on silica gel, eluting with hexanes/ethyl acetate 4:1 and then 2:1, yielded **23** (60 mg, 0.16 mmol, 74%) as an inseparable 1.6:1 mixture of diastereomers: $R_f = 0.38$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3456, 1732 (br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95−5.80 (m, 1H), 5.39−5.20 (m, 2H), 4.70−4.65 (m, 2H), 4.28−4.18 (m, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 2.96−2.73 (m, 2H), 2.68−2.55 (m, 1H), 2.40 (dd, 1H, $J = 16.4, 8.5$ Hz), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 167.9, 167.3, 167.1, 166.6, 164.6, 130.9, 119.2, 85.2, 67.2, 67.0, 58.7, 58.7, 54.2, 53.7, 53.6, 51.9, 37.1, 37.1, 31.1, 31.1, 27.3; HRMS calcd for $C_{17}H_{26}NO_8$ 372.1658, found 372.1649.

General Procedure for the $Pd(OAc)_2$-Catalyzed Decarboxylation of Allyl Esters. $Pd(OAc)_2$ (0.1 equiv) and PPh_3 (0.2 equiv) were weighed into a dry round-bottom flask equipped with a stir bar and capped with a rubber septum. MeCN was added, and the mixture stirred for 10 min. $PhSiH_3$ (2−3 equiv) was added and the mixture stirred for 10 min. To this dark brown mixture was added the allyl ester substrate (1 equiv) in MeCN with a cannula. After the mixture stirred at room temperature for 30−120 min, it was concentrated under reduced pressure, applied to a column containg silica gel, and eluted with a mixture of hexanes and EtOAc.

General Procedure for the Pd/C-Catalyzed Decarboxylation of Benzyl Esters. The benzyl ester substrate (1 equiv) and Pd/C (10%, 80 mg/mmol substrate) were weighed into a dry round-bottom flask equipped with a stir bar and capped with a rubber septum. MeCN was added, and a balloon of H_2 gas was attached. The reaction stirred a room temperature for 20−120 min. The catalyst was removed by filtration through a pad of Celite. After concentration under reduced pressure, the product was purified by flash chromatography on silica gel eluting with hexanes and EtOAc.

***N*-*tert*-Butoxy-2-methylmalonamic *tert*-Butyl Ester (24).** According to the general procedure for decarboxylation with $Pd(OAc)_2$, **13** (50 mg, 0.152 mmol) was decarboxylated by stirring for 1 h with $Pd(OAc)_2$ (2 mg, 0.0076 mmol), PPh_3 (4 mg, 0.0152 mmol), and $PhSiH_3$ (49 mg, 0.456 mmol) in MeCN (3 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 5:1 and then 1:1 to yield **24** (37 mg, 0.148 mmol, 98%): $R_f = 0.05$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3198, 1740, 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 3.17 (q, 1H, $J = 5.7, 4.9$ Hz), 1.47 (s, 9H), 1.39 (d, 3H, $J = 5.4, 1.3$ Hz), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.2, 82.5, 82.3, 46.4, 27.9, 26.2, 15.1; HRMS calcd for $C_{12}H_{24}NO_4$ 246.1697, found 246.1705.

2-*tert*-Butoxycarbamoylbut-3-enoic Acid Ethyl Ester (25). According to the general procedure for decarboxylation with $Pd(OAc)_2$, **20** (20 mg, 0.061 mmol) was decarboxylated by stirring for 1 h with $Pd(OAc)_2$ (1.4 mg, 0.0061 mmol), PPh_3 (3.2 mg, 0.0122 mmol), and $PhSiH_3$ (20 mg, 0.183 mmol) in MeCN (3 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 3:1, 1:1, to yield **25** (16 mg, 0.59 mmol, 97%): $R_f = 0.26$ on silica gel (3:1 hexanes/ethyl acetate); IR (neat) 3192, 1743, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 5.80−5.63 (m, 1H), 5.15−5.03 (m, 2H), 4.17 (q, 2H, $J = 14.2, 7.1$ Hz), 3.26 (t, 1H, $J = 14.4, 7.4$ Hz), 2.67 (t, 2H, $J = 14.3, 7.2$ Hz), 1.26 (s, 9H), 1.26 (t, 3H, $J = 14.3, 7.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 166.6, 133.6, 118.2, 82.5, 61.8, 51.0, 34.2, 26.2, 14.1; HRMS calcd for $C_{12}H_{23}NO_4$ 244.1548, found 244.1541.

***N*-*tert*-Butoxy-2-benzylmalonic Acid Methyl Ester (26).** According to the general procedure for decarboxylation with $Pd(OAc)_2$, **21** (13.5 mg, 0.037 mmol) was decarboxylated by

stirring for 1 h with $Pd(OAc)_2$ (1 mg, 0.0045 mmol), PPh_3 (2.4 mg, 0.009 mmol), and $PhSiH_3$ (12 mg, 0.111 mmol) in MeCN (2 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 2:1, 1:1 to yield **26** (10 mg, 0.036 mmol, 98%). Alternatively, **26** was decarboxylated with Pd/C (4 mg) and H_2 to yield the same product (13 mg, 0.476 mmol, 98%): $R_f = 0.23$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3196, 1746, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.30−7.15 (m, 5H0, 3.68 (s, 3H), 3.42 (t, 1H, $J = 14.7$, 7.5 Hz), 7.32−7.16 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 166.4, 137.5, 128.9, 128.4, 126.9, 82.6, 53.0, 52.6, 35.4, 26.1; HRMS calcd for $C_{15}H_{22}NO_4$ 280.1548, found 280.1540.

2-*tert*-Butoxycarbamoyl-4-phenylbut-3-enoic Acid Methyl Ester (27). According to the general procedure for decarboxylation with $Pd(OAc)_2$, **22** (18.3 mg, 0.047 mmol) was decarboxylated by stirring for 2 h with $Pd(OAc)_2$ (1.1 mg, 0.0047 mmol), PPh_3 (2.5 mg, 0.0094 mmol), and $PhSiH_3$ (15 mg, 0.141 mmol) in MeCN (2 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 2:1 and then 1:1 to yield **27** (12 mg, 0.0393 mmol, 84%): $R_f = 0.23$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3208, 1745, 1664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.31−7.15 (m, 5H), 6.45 (d, 1H, $J = 15.8$ Hz), 6.13−6.01 (m, 1H), 3.73 (s, 3H), 3.33 (t, 1H, 14.6, 7.2 Hz), 2.85−2.75 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.5, 136.8, 133.4, 128.5, 127.5, 126.2, 124.9, 82.6, 52.7, 51.2, 33.4, 26.2; HRMS calcd for $C_{17}H_{24}NO_4$ 306.1705, found 306.1696.

***N*-*tert*-butoxymalonamic Acid Methyl Ester (28).** According to the general procedure for decarboxylation with Pd/C, **9** (150 mg, 0.464 mmol) was decarboxylated by stirring under H_2 for 20 min with Pd/C (28 mg) in MeCN (5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 3:1 and then 2:1 to yield **28** (81.2 mg, 0.43 mmol, 93%): $R_f = 0.09$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3208, 1748, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 3.63 (s, 3H), 3.24 (s, 2H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 163.7, 82.3, 52.5, 39.8, 26.1; HRMS calcd for $C_8H_{16}NO_4$ 190.1070, found 190.1079.

***N*-*tert*-butoxy-2-methylmalonamic Acid Methyl Ester (29).** According to the general procedure for decarboxylation with Pd/C, **10** (105 mg, 0.313 mmol) was decarboxylated by stirring under H_2 for 20 min with Pd/C (27 mg) in MeCN (5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 5:1 and then 2:1 to yield **29** (63 mg, 0.31 mmol, 98%): $R_f = 0.11$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3209, 1749, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 3.73 (s, 3H), 3.29 (dd, 1H, $J = 7.7$, 7.2 Hz), 1.43d, 3H, $J = 7.7$ Hz), 1.26 (s, 9H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 167.8, 82.4, 52.7, 44.9, 26.2, 14.7; HRMS calcd for $C_9H_{18}NO_4$ 204.1214, found 204.1235.

2-Oxocyclopentanecarboxylic Acid *tert*-Butoxyamide (30). According to the general procedure for decarboxylation with Pd/C, 1-*tert*-butoxycarbamoyl-2-oxocyclopentanecarboxylic acid benzyl ester (39 mg, 0.117 mmol) was decarboxylated by stirring under H_2 for 2 h with Pd/C (9.5 mg) in MeCN (3 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 3:1 and then 2:1 to yield **30** (14 mg, 0.07 mmol, 61%): $R_f = 0.09$ on silica gel (2:1 hexanes/ethyl acetate); IR (neat) 3216, 1747, 1664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 2.99 (t, 1H, $J = 17.7$, 8.9 Hz), 2.42−2.19 (m, 4H), 2.13−2.05 (m, 1H), 1.92−1.78 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 166.0, 82.1, 53.1, 38.6, 26.2, 25.5, 20.7; HRMS calcd for $C_{10}H_{18}NO_3$ 200.1286, found 200.1293.

1-*tert*-Butoxy-5-methoxycarbonylmethyl-2-oxo-pyrrolidine-3-carboxylic Acid Methyl Ester (31). According to the general procedure for decarboxylation with $Pd(OAc)_2$, **23** (55 mg, 0.148 mmol) was decarboxylated by stirring for 1 h with $Pd(OAc)_2$ (3.3 mg, 0.0148 mmol), PPh_3 (8 mg, 0.0296 mmol), and $PhSiH_3$ (34 mg, 0.311 mmol) in MeCN (5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc 2:1 and then 1:1 to yield **31** as an inseparable 2.2:1 mixture of diastereomers (28.4 mg, 0.099 mmol, 67%): $R_f = 0.30$ on silica gel (2:1 hexanes:ethyl acetate); IR (neat) 3457, 1726 (br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26−4.16 (1H, m), 3.78 and 3.77 (s, 3H), 3.70 (s, 3H), 3.45−3.36 (m, 1H), 2.99 and 2.84 (dd, 1H, $J = 20.8$, 16.0 Hz), 2.70−2.46 (m, 2H), 2.35 (dd, 1H, $J = 15.9$, 8.1 Hz), 2.26−2.04 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.0, 170.1, 168.2, 84.7, 84.5, 55.7, 55.3, 52.9, 51.9, 43.6, 43.4, 37.3, 36.2, 27.2, 25.4, 24.9; HRMS calcd for $C_{13}H_{22}NO_6$ 288.1447, found 288.1437.

General Procedure for Acid Cleavage of the *tert*-Butyl Group from *O*-*t*-Butoxycarbonylamino Compounds. The *O*-*t*-butoxycarbonylamino compound was dissolved in CH_2Cl_2, and fresh trifluoroacetic acid (11 mL/mmol of substrate) was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 48 h. The solvent was evaporated, and the product was purified by flash chromatography on silica gel eluting with mixtures of hexanes and EtOAc.

2-Hydroxycarbamoylmalonic Acid Dimethyl Ester (32). According to the general procedure, **5** (23 mg, 0.093 mmol) was stirred with TFA (1 mL) in CH_2Cl_2 (1.5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate 1:1 to yield **32** (13.4 mg, 0.07 mmol, 75%): $R_f = 0.34$ on silica gel (1:1 hexanes/ethyl acetate); IR (neat) 3457, 1726 (br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26−4.16 (1H, m), 3.78 and 3.77 (s, 3H), 3.70 (s, 3H), 3.45−3.36 (m, 1H), 2.99 and 2.84 (dd, 1H, $J = 20.8$, 16.0 Hz), 2.70−2.46 (m, 2H), 2.35 (dd, 1H, $J = 15.9$, 8.1 Hz), 2.26−2.04 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.0, 170.1, 168.2, 84.7, 84.5, 55.7, 55.3, 52.9, 51.9, 43.6, 43.4, 37.3, 36.2, 27.2, 25.4, 24.9; HRMS calcd for $C_6H_{10}NO_6$ 192.0508, found 192.0502.

2-Hydroxycarbamoylmalonic Acid Allyl Ester Methyl Ester (33). According to the general procedure, **12** (23 mg, 0.093 mmol) was stirred with TFA (1 mL) in CH_2Cl_2 (1.5 mL) for 48 h. The product was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate 1:1 to yield **33** (15 mg, 0.07 mmol, 76%) as a white solid: $R_f = 0.15$ on silica gel (1:1 hexanes/ethyl acetate); mp 32−34 °C; IR (neat) 3307, 1742, 1678 (br) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.8 (1H, brs), 5.90−5.70 (1H, m), 5.30−5.15 (2H, m), 4.61 (2H, d, $J = 5.9$ Hz), 4.38 91H, s), 3.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 164.4, 160.2, 130.6, 119.6, 67.4, 56.9, 53.8; HRMS calcd for $C_8H_{12}NO_6$ 218.0664, found 218.0672.

2-Hydroxycarbamoyl-2-benzylmalonic Acid Allyl Ester Methyl Ester (34). According to the general procedure, **26** (35 mg, 0.096 mmol) was stirred with TFA (1 mL) in CH_2Cl_2 (1.5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate 1:1 to yield **34** (20.0 mg, 0.065 mmol, 68%): $R_f = 0.42$ on silica gel (1:1 hexanes/ethyl acetate); IR (neat) 3336, 1764, 1734, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.39 (1H, brs), 7.25−7.19 (3H, m), 7.03−6.95 (2H, m), 5.90−5.75 (1H, m) 5.33−5.21 (2H, m), 4.64 (2H, d, $J = 5.6$ Hz), 3.76 (3H, s), 3.60 (2H, s)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 166.8, 162.3, 134.1, 130.6, 129.4, 128.6, 127.7, 119.5, 67.1, 64.1, 53.5, 40.1; HRMS calcd for $C_{15}H_{18}NO_6$ 308.1134, found 308.1124.

2-Hydroxycarbamoyl-2-methylmalonic Acid Diethyl Ester (35). According to the general procedure, **6** (40 mg, 0.138 mmol) was stirred with TFA (1.5 mL) in CH_2Cl_2 (1.5 mL). The product was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate 1:1 to yield **35** (21 mg, 0.09 mmol, 65%): $R_f = 0.34$ on silica gel (1:1 hexanes/ethyl acetate); IR (neat) 3338, 25, 1733, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18−10.0 (1H, brs), 4.10 (dd, $J = 14.2$, 7.1 Hz, 4H), 1.72 (s, 3H), 1.25 (t, $J = 12.2$, 7.1 Hz. 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 164.8, 62.8, 29.7, 20.6, 13.8; HRMS calcd for $C_9H_{16}NO_6$ 234.0977, found 234.0969.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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