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One-Step Formation both of C–N and of C–O Bonds of *N*-Alkoxyamides through NHC-Catalyzed Three-Component Reactions of Enals, Nitrosoarenes, and Enones

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NHC-catalyzed three-component reactions of α,β-unsaturated aldehydes (enals), nitrosoarenes, and α,β-unsaturated ketones (enones) were studied. The reactions proceeded through a cascade aza-benzoin condensation/oxo-Michael addition sequence to produce *N*,*O*-bisfunctionalized *N*-hydroxylacrylamides in moderate to good yields. This work not only provides an efficient method for the one-step formation both of the C–N and of the C–O bonds in *N*-alkoxyamides, but also advances the application of NHC organocatalysis in the field of multicomponent reactions.

Introduction

Reactions catalyzed by N-heterocyclic carbenes (NHCs) have emerged as an exceptionally fruitful research area in organic chemistry in recent years.[1] Most NHC-catalyzed reactions are initiated by umpolung of electrophilic aldehyde carbonyl groups into nucleophiles through the action of a heterocyclic carbene. The interactions between NHCs and saturated aldehydes or aryl aldehydes to form Breslow intermediates belong to the a^1–d^1 class of umpolung (a^1 to d^1 umpolung) according to the terminology of Seebach.[2] The classical examples of reactions of this type are benzoin reactions between d^1-nucleophiles and aldehydes[1,3] or Stetter reactions between d^1-nucleophiles and Michael acceptors.[1,4] The action of NHCs on α,β-unsaturated aldehydes (enals), on the other hand, generally results in the formation of homoenolate intermediates that can be regarded as d^3-nucleophiles and thus constitute a^3–d^3 umpolung. The homoenolate intermediates produced from α,β-unsaturated aldehydes and NHCs, for example, acted as carbon nucleophiles at the β-positions of carbonyls to react with aldehydes or ketones leading to the formation of γ-butyrolactones,[5] whereas the homoenolates of α,β-unsaturated aldehydes reacted with imines to produce γ-lactams.[6] NHC-catalyzed homoenolate annulations of α,β-unsaturated aldehydes (enals) with α,β-unsaturated ketones (enones) generally formed cyclopentane skeletons to afford cyclopentenes, cyclopentanols, or cyclopentanones.[7] Although numerous NHC-catalyzed reactions have been documented in the literature, and multicomponent reactions (MCRs) incorporating NHCs have also been well explored,[8] studies on NHC-catalyzed MCRs are very rare.[9,10a]

In recent years a few NHC-catalyzed reactions between carbonyl compounds and nitrosoarenes have been reported; these provided an efficient method for the formation of carbon-nitrogen bonds.[11–12] For instance, whereas Breslow intermediates derived from aldehydes and NHCs reacted with nitrosoarenes leading to the direct amidation of aldehydes to provide *N*-arylhydroxamic acids,[10a] the NHC-catalyzed cascade reactions between *o*-vinylarylaldehydes and nitrosoarenes produced 2,3-benzoxazin-4-one derivatives.[10b] On the other hand, the homoenolate intermediates produced from α,β-unsaturated aldehydes and NHCs underwent cascade nucleophilic additions and intramolecular cyclizations with nitrosoarenes to afford isoxazolidin-5-one products or intermediates, which could further convert into isoxazol-5-ones, β-amino acid esters, or benzo[*b*][1,4]oxazepin-2-ones.[11] NHC-catalyzed reactions between ketenes and nitrosoarenes proceeded through formal [2+2] cycloadditions to produce oxazetidinones.[12]

We have been interested in the reactivity of *N*-heterocyclic carbenes and their versatility in organic syntheses for many years.[13] Recently our attention was drawn to NHC-catalyzed reactions.[10b,14] NHC organocatalysis has only rarely been utilized in promoting multicomponent reactions, so we considered that the development of NHC-catalyzed multicomponent reactions could be of great importance for the establishing of highly efficient synthetic methods. We were intrigued by multicomponent reactions of enals, enones, and nitroso compounds in terms of various possible reaction pathways, and envisioned that the reactions could lead to interesting multifunctional compounds. Here

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we report our investigation into three-component reactions of α,β-unsaturated aldehydes, nitrosoarenes, and α,β-unsaturated ketones, which provide an efficient one-pot method for the synthesis of *N*,*O*-bisfunctionalized *N*-hydroxylacrylamides.

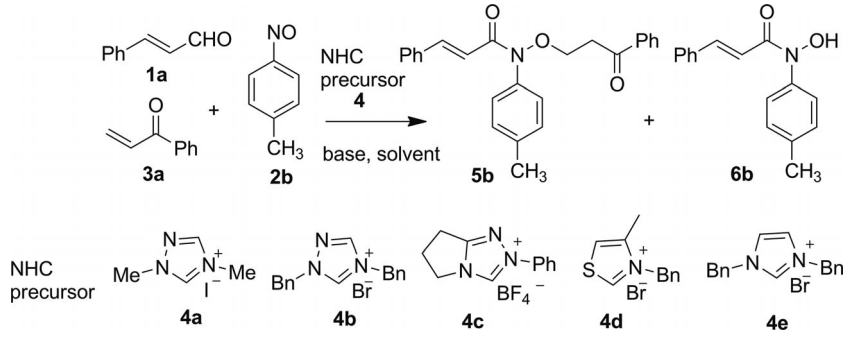
Results and Discussion

Initially, the reaction of cinnamaldehyde (**1a**, Table 1), 1-methyl-4-nitrosobenzene (**2b**), and 1-phenylprop-2-en-1-one (**3a**) (**1a**/**2b**/**3a** 1:1:1.5) catalyzed by different NHCs **4′** (20 mol-%, generated in situ from the corresponding azolium salts **4** with a base) in dry dichloromethane was examined at 25–30 °C. It was found that triazole carbenes **4a′**, **4b′**, and **4c′** could promote this reaction to produce **5b** in 54%, 73%, and 30% yields, respectively, along with 11–25% yields of by-product **6b** (Table 1, Entries 1–3). In contrast, when the reaction was performed under the same conditions but in the presence of imidazole carbene **4c′** or thiazole carbene **4d′** it was inefficient.

The reaction conditions with catalysis by triazole carbene **4b′** were further optimized by variation of catalyst loadings, ratios of starting materials, temperature, solvents, and bases used to generate the carbene catalyst. In dichloromethane, halving the catalyst loading to 10 mol-% led to the formation of **5b** in 63% yield (Table 1, Entry 6). Increases in the equivalents of **1a** or **2b** all decreased the yield of major product **5b**, whereas utilization of 2 equiv. of enone **3a** gave yields of **5b** and **6a** very similar to those of the reaction in the presence of 1.5 equiv. of enone **3a** (Table 1, Entries 2, 7–10). Use of lower or higher reaction temperatures, of other solvents (including acetonitrile, THF, dioxane, and benzene), and of other bases (such as *t*BuOK, Cs_2CO_3, NaH, and Hünig's base) all caused reduced yields of product **5b** (Table 1, Entries 11–20).

Because the use of larger excesses of enone **3a** did not significantly improve the yield of major product **5b**, 1.5 equiv. of enones **3** were employed in other reactions, to save starting materials. The scope of the reaction under the optimized conditions was studied by use of a variety of substituted α,β-unsaturated aldehydes **1**, nitroso compounds **2**, and α,β-unsaturated ketones **3** (Table 2). It was found that the reaction showed tolerance for the substituents attached to cinnamaldehydes **1**. All cinnamaldehydes **1a**–**1e**, substituted either with electron-donating or with electron-withdrawing groups, reacted with 1-methoxy-4-nitrosobenzene (**2c**) and 1-phenylprop-2-en-1-one (**3a**) to produce 3-aryl-*N*-(*p*-methoxyphenyl)-*N*-(3-oxo-3-phenylpropoxy)acrylamides **5** in 63–72% yields, along with 9–24% yields of 3-aryl-*N*-hydroxyl-*N*-(*p*-methoxyphenyl)acrylamides **6** (Table 2, En-

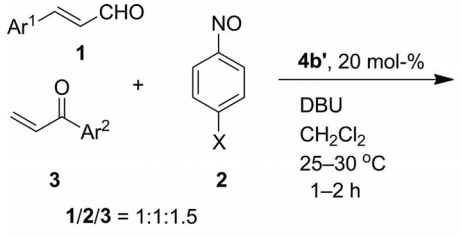
Table 1. Optimization of the reaction conditions.

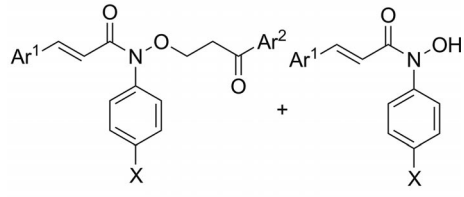


Entry	**1a**/**2b**/**3a**	NHC precursor **4**	mol-% of **4**	Base	Solvent	Temperature [°C]	Time [h]	Yield [%] **5b**	**6b**
1	1:1:1.5	**4a**	20	DBU	CH_2Cl_2	25–30	4	54	23
2	**1:1:1.5**	**4b**	**20**	**DBU**	**CH_2Cl_2**	**25–30**	**2**	**73**	**11**
3	1:1:1.5	**4c**	20	DBU	CH_2Cl_2	25–30	5	30	25
4	1:1:1.5	**4d**	20	DBU	CH_2Cl_2	25–30	5	4	14
5	1:1:1.5	**4e**	20	DBU	CH_2Cl_2	25–30	5	12	19
6	1:1:1.5	**4b**	10	DBU	CH_2Cl_2	25–30	2	63	17
7	1:1:1	**4b**	20	DBU	CH_2Cl_2	25–30	2	49	18
8	1.5:1:1	**4b**	20	DBU	CH_2Cl_2	25–30	2	64	16
9	1:1.5:1	**4b**	20	DBU	CH_2Cl_2	25–30	2	62	19
10	**1:1:2**	**4b**	**20**	**DBU**	**CH_2Cl_2**	**25–30**	**2**	**74**	**10**
11	1:1:1.5	**4b**	20	DBU	CH_2Cl_2	0	12	64	19
12	1:1:1.5	**4b**	20	DBU	CH_2Cl_2	reflux	2	59	20
13	1:1:1.5	**4b**	20	DBU	CH_3CN	25–30	2	66	13
14	1:1:1.5	**4b**	20	DBU	THF	25–30	2	44	34
15	1:1:1.5	**4b**	20	DBU	dioxane	25–30	2	52	25
16	1:1:1.5	**4b**	20	DBU	benzene	25–30	2	53	21
17	1:1:1.5	**4b**	20	*t*BuOK	CH_2Cl_2	25–30	2	34	33
18	1:1:1.5	**4b**	20	Cs_2CO_3	CH_2Cl_2	25–30	2	11	25
19	1:1:1.5	**4b**	20	NaH	CH_2Cl_2	25–30	2	38	33
20	1:1:1.5	**4b**	20	DIPEA	CH_2Cl_2	25–30	2	14	22

tries 3, 10–13). On the other hand, although all nitrosoarenes **2** and enones **3** substituted with anisyl, tolyl, phenyl, or halophenyl groups reacted with cinnamaldehyde (**1a**) smoothly to produce compounds **5** in 54–73% yields (Table 2, Entries 1–4, 6–8), the three-component reactions either with 1-nitro-4-nitrosobenzene (**2e**) or with 1-(4-nitrophenyl)prop-2-en-1-one (**3e**) as one of the reactants did not form products **5** or **6** (Table 2, Entries 5 and 9). The inefficiency of the nitro-substituted nitrosobenzene **2e** or enone **3e** in the three-component reactions with enals **1** was probably due to their instability in the presence of triazole carbene and DBU. Because the products **5** were presumably derived from the addition of by-products **6** to enones **3**, promotion of the transformation of compounds **6** to compounds **5** was attempted, variously by utilization of more enones **3** or base (DBU), prolongation of reaction time, or elevation of reaction temperature. However, none of them could improve the yields of **5**. After the occasional discovery that products **5** would undergo base-catalyzed elimination to give products **6** and enones **3** in the presence of DBU, we realized that the formation of **5** from **6** and **3** is actually a reversible process. We were therefore now able to understand why byproducts **6** could not be totally transformed into products **5** under the reaction conditions.

Table 2. Reactions of enals **1**, nitrosoarenes **2**, and enones **3** under the optimized conditions.

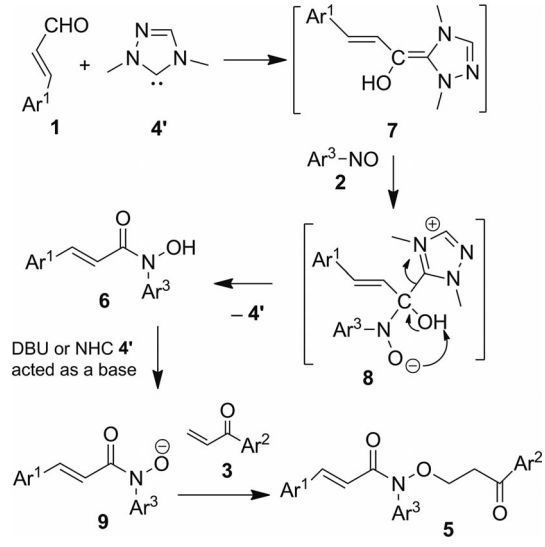




Entry	1	Ar^1	2	X	3	Ar^2	Yield [%]
1	**1a**	Ph	**2a**	H	**3a**	Ph	**5a** [54], **6a** [15]
2	**1a**	Ph	**2b**	Me	**3a**	Ph	**5b** [73], **6b** [11]
3	**1a**	Ph	**2c**	OMe	**3a**	Ph	**5c** [72], **6c** [9]
4	**1a**	Ph	**2d**	Cl	**3a**	Ph	**5d** [54], **6d** [27]
5	**1a**	Ph	**2e**	NO_2	**3a**	Ph	–
6	**1a**	Ph	**2c**	OMe	**3b**	*p*-MePh	**5e** [64], **6e** [15]
7	**1a**	Ph	**2c**	OMe	**3c**	*p*-MeOPh	**5f** [67], **6f** [18]
8	**1a**	Ph	**2c**	OMe	**3d**	*p*-BrPh	**5g** [58], **6g** [13]
9	**1a**	Ph	**2c**	OMe	**3e**	*p*-NO_2Ph	–
10	**1b**	*p*-MePh	**2c**	OMe	**3a**	Ph	**5i** [67], **6i** [24]
11	**1c**	*p*-MeOPh	**2c**	OMe	**3a**	Ph	**5j** [64], **6j** [17]
12	**1d**	*p*-BrPh	**2c**	OMe	**3a**	Ph	**5k** [71], **6k** [15]
13	**1e**	*p*-NO_2Ph	**2c**	OMe	**3a**	Ph	**5l** [63], **6l** [18]

The structures of products were elucidated on the basis of spectroscopic data and microanalysis. The NMR spectra, mass data, and elemental analyses indicated that the major products **5** are 3-aryl-*N*-aryl-*N*-(3-oxo-3-arylpropoxy)acrylamides derived from the 1+1+1 addition of enals **1** with nitroso compounds **2** and enones **3**, whereas the minor products **6** are 3-aryl-*N*-aryl-*N*-hydroxylacrylamides that are adducts of **1** with **2**. To identify the products beyond doubt, the structure of **5i** was also determined by single-crystal X-ray diffraction analysis.[15]

A cascade mechanism for these three-component reactions is proposed (Scheme 1). Unlike in most NHC-catalyzed reactions of α,β-unsaturated aldehydes, in which the enals are believed to be converted into homoenolate intermediates and to act as γ-carbon nucleophiles, here the α,β-unsaturated aldehydes **1** are believed to form Breslow intermediates **7** with NHC and to behave as α-carbon nucleophiles toward nitrosoarenes **2** to produce intermediates **8**. Proton shifting from C–OH to N–OH, accompanied by the elimination of the NHC moiety from **8**, would produce products **6**. With catalysis by a base such as DBU or triazole carbene **4′**, oxo-Michael addition of *N*-hydroxylacrylamides **6** to α,β-unsaturated ketones **3** would afford products **5**. N-Heterocyclic carbenes have been reported to catalyze conjugate additions of alcohols to α,β-unsaturated ketones,[16] and we have also verified the transformation of compounds **6** into **5** by treatment of **6** with enones **3** in the presence of DBU. These studies support our mechanism. Theoretically, the Breslow intermediates derived from α,β-unsaturated aldehydes and NHCs could undergo Michael addition to α,β-unsaturated ketones to form 1,4-diketones (Stetter reaction). Additionally, cinnamaldehydes **1** have been reported to form homoenolate intermediates with an imidazole carbene, afterwards undergoing Michael addition with α,β-unsaturated ketones to produce cyclopentanols.[7b] However, no such products derived from enals **1** and enones **3** were isolated from this three-component reaction. Examination of the reaction behavior between α,β-unsaturated al-



Scheme 1. Proposed mechanism.

dehydes **1** and α,β-unsaturated ketones **3** in the absence of nitrosoarenes **2** under the same conditions as used in the three-component reactions showed that the interaction of enals **1** with enones **3** was actually inefficient under our reaction conditions.

Conclusions

In summary, we have studied NHC-catalyzed three-component reactions of α,β-unsaturated aldehydes, nitrosoarenes, and α,β-unsaturated ketones. The reactions proceeded by cascade aza-benzoin condensations between α,β-unsaturated aldehydes and nitrosoarenes, followed by oxo-Michael additions of the *N*-hydroxylacrylamide to the α,β-unsaturated ketones to produce *N*,*O*-functionalized *N*-hydroxylacrylamides in moderate to good yields. This work not only provides an efficient method for the one-step construction of both C–N and C–O bonds of *N*-alkoxyamides, but also advances the application of NHC organocatalysis in the field of multicomponent reactions.

Experimental Section

General: Melting points were determined with a Reliant YRT-3 melting point apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in the indicated solvents. *J* values are reported in Hz. IR spectra were recorded with an AVATAR 360 FT-IR spectrometer. Mass spectra were recorded with a Surveyor MSQ Plus (ESI) instrument and elemental analyses were performed with a GMBH Vario EL instrument. Column chromatography was performed with 200–300 mesh silica gel. The NHC precursors **4a**,[17] **4b**,[18] **4c**,[19] **4d**,[18] and **4e**[18] were prepared by literature methods.

General Procedure for the Reactions of α,β-Unsaturated Aldehydes 1, Nitrosoarenes 2, and α,β-Unsaturated Ketones 3: An α,β-unsaturated aldehyde **1**[20] (1 mmol), a nitrosoarene **2**[21] (1 mmol), an α,β-unsaturated ketone **3**[22] (1.5 mmol), and an *N*,*N*-dimethyl-1,2,4-triazolium salt (0.2 mmol) were mixed in dry dichloromethane (12 mL) under nitrogen at 25–30 °C. DBU (0.2 mmol) was then added, and the mixture was stirred at about 25 °C for 4–6 h. The solvent was removed under vacuum and the residue was chromatographed on a silica gel column with elution with a mixture of petroleum ether and ethyl acetate (10:1 to 2:1) to afford the corresponding products **5** and **6**.

***N*-(3-Oxo-3-phenylpropoxy)-*N*-phenylcinnamamide (5a):** This compound was obtained in 54% yield (203 mg); m.p. 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.3 Hz, 2 H, ArH), 7.80 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.65 (d, *J* = 6.7 Hz, 2 H, ArH), 7.57–7.60 (m, 3 H, ArH), 7.47 (t, *J* = 7.8 Hz, 2 H, ArH), 7.37–7.44 (m, 6 H, ArH, C=CH), 7.26 (d, *J* = 8.3 Hz, 1 H, ArH), 4.42 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.37 (t, *J* = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 165.7, 144.3, 138.8, 136.6, 135.2, 133.5, 129.9, 128.9, 128.8, 128.7, 128.3, 128.1, 126.6, 123.2, 117.3, 69.3, 36.5 ppm. IR: $\tilde{\nu}$ = 1684, 1667, 1620 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{22}NO_3$ $[M + H]^+$ 372.1591; found 372.1591.

***N*-(3-Oxo-3-phenylpropoxy)-*N*-(*p*-tolyl)cinnamamide (5b):** This compound was obtained in 73% yield (281 mg); m.p. 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.2 Hz, 2 H, ArH), 7.78 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.62 (br, 2 H, ArH), 7.58 (t, *J* = 7.4 Hz, 1 H, ArH), 7.47 (t, *J* = 7.8 Hz, 2 H, ArH), 7.33–7.43 (m, 6 H, ArH, C=CH), 7.21 (d, *J* = 8.2 Hz, 2 H, ArH), 4.40 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.36 (t, *J* = 6.6 Hz, 2 H, CH_2), 2.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 165.5, 143.9, 136.8, 136.6, 136.2, 135.3, 133.5, 129.8, 129.5, 128.8, 128.7, 128.3, 128.1, 123.7, 117.4, 69.1, 36.5, 21.0 ppm. IR: $\tilde{\nu}$ = 1689, 1669, 1627 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{24}NO_3$ $[M + H]^+$ 386.1756; found 386.1750.

***N*-Hydroxy-*N*-(*p*-tolyl)cinnamamide (6b):** This compound was obtained in 11% yield (28 mg); m.p. 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.39–7.41 (m, 2 H, ArH), 7.32–7.33 (m, 5 H, ArH), 7.26 (d, *J* = 9.1 Hz, 2 H, ArH), 6.51 (d, *J* = 15.2 Hz, 1 H, C=CH), 2.42 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 142.7, 139.2, 135.3, 134.8, 129.9, 128.8, 128.0, 126.4, 115.4, 21.2 ppm. IR: $\tilde{\nu}$ = 3130, 1638, 1587, 1575 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{16}NO_2$ $[M + H]^+$ 254.1181; found 254.1185.

***N*-(*p*-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropoxy)cinnamamide (5c):** This compound was obtained in 72% yield (292 mg); m.p. 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.4 Hz, 2 H, ArH), 7.76 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.61 (br, 2 H, ArH), 7.58 (t, *J* = 7.3 Hz, 1 H, ArH), 7.47 (d, *J* = 7.8 Hz, 2 H, ArH), 7.45 (t, *J* = 8.5 Hz, 2 H, ArH), 7.33–7.41 (m, 4 H, ArH, C=CH), 6.93 (d, *J* = 8.9 Hz, 2 H, ArH), 4.40 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.36 (t, *J* = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 158.7, 143.8, 136.6, 135.2, 134.9, 133.5, 131.6, 129.8, 128.8, 128.7, 128.3, 128.1, 127.9, 117.3, 114.3, 69.0, 55.6, 36.6 ppm. IR: $\tilde{\nu}$ = 1689, 1650, 1613 cm^{-1}. MS (ESI): *m*/*z* = 402 $[M + H]^+$. $C_{25}H_{23}NO_4$: C 74.79, H 5.77, N 3.49; found C 74.47, H 5.90, N 3.29.

***N*-Hydroxy-*N*-(*p*-methoxyphenyl)cinnamamide (6c):** This compound was obtained in 9% yield (24 mg); m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.32–7.40 (m, 8 H, ArH), 6.99 (d, *J* = 8.7 Hz, 2 H, ArH), 6.43 (d, *J* = 15.3 Hz, 1 H, C=CH), 3.87 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 160.2, 142.6, 134.7, 130.1, 130.0, 128.8, 128.7, 128.0, 115.0, 114.6, 55.6 ppm. IR: $\tilde{\nu}$ = 3119, 1641, 1592, 1578 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{16}NO_3$ $[M + H]^+$ 270.1130; found 270.1132.

***N*-(*p*-Chlorophenyl)-*N*-(3-oxo-3-phenylpropoxy)cinnamamide (5d):** This compound was obtained in 54% yield (219 mg); m.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.3 Hz, 2 H, ArH), 7.80 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.68 (d, *J* = 6.2 Hz, 2 H, ArH), 7.60 (t, *J* = 7.5 Hz, 1 H, ArH), 7.56 (d, *J* = 8.8 Hz, 2 H, ArH), 7.48 (t, *J* = 7.8 Hz, 2 H, ArH), 7.33–7.44 (m, 6 H, ArH, C=CH), 4.41 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.37 (d, *J* = 5.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 165.8, 144.9, 137.4, 136.5, 135.1, 133.6, 131.6, 130.1, 128.9, 128.81, 128.76, 128.4, 128.1, 123.9, 116.9, 69.4, 36.4 ppm. IR: $\tilde{\nu}$ = 1685, 1655, 1614 cm^{-1}. MS (ESI): *m*/*z* = 428 $[M + Na]^+$. $C_{24}H_{20}ClNO_3$ (405.88): calcd. C 71.02, H 4.97, N 3.45; found C 70.70, H 5.12, N 3.29.

***N*-(*p*-Methoxyphenyl)-*N*-[3-oxo-3-(*p*-tolyl)propoxy]cinnamamide (5e):** This compound was obtained in 64% yield (266 mg); m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.1 Hz, 2 H, ArH), 7.76 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.61 (br, 2 H, ArH), 7.44 (d, *J* = 8.1 Hz, 2 H, ArH), 7.36–7.40 (m, 4 H, ArH, C=CH), 7.25 (d, *J* = 7.8 Hz, 2 H, ArH), 6.94 (d, *J* = 8.6 Hz, 2 H, ArH), 4.39 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.33 (t, *J* = 5.8 Hz, 2 H, CH_2), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4, 165.6, 158.6, 144.4, 143.7, 135.3, 134.2, 131.6, 129.8, 129.40, 129.35, 128.7, 128.2, 125.9, 117.3, 114.2, 69.1, 55.6,

36.4, 21.7 ppm. IR: ṽ = 1683, 1650, 1613 cm^{-1}. MS (ESI): *m*/*z* = 416 [M + H]$^+$. $C_{26}H_{25}NO_4$ (415.49): calcd. C 75.16, H 6.06, N 3.37; found C 74.72, H 5.95, N 3.22.

***N*-(*p*-Methoxyphenyl)-*N*-[3-(*p*-methoxyphenyl)-3-oxopropoxy]-cinnamamide (5f):** This compound was obtained in 67% yield (289 mg); m.p. 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.8 Hz, 2 H, ArH), 7.75 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.60 (br, 2 H, ArH), 7.34–7.45 (m, 6 H, ArH, C=CH), 6.94 (d, *J* = 8.9 Hz, 2 H, ArH), 6.92 (d, *J* = 8.8 Hz, 2 H, ArH), 4.39 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.30 (t, *J* = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 163.8, 158.6, 143.7, 135.3, 131.6, 130.4, 129.8, 128.7, 128.3, 126.0, 117.4, 114.2, 113.9, 69.2, 55.54, 55.46, 36.2 ppm. IR: ṽ = 1679, 1659, 1619 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{26}NO_5$ [M + H]$^+$ 432.1811; found 432.1802.

***N*-[3-(*p*-Bromophenyl)-3-oxopropoxy]-*N*-(*p*-methoxyphenyl)-cinnamamide (5g):** This compound was obtained in 58% yield (284 mg); m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.5 Hz, 2 H, ArH), 7.75 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.59 (d, *J* = 8.5 Hz, 2 H, ArH), 7.58 (br, 2 H, ArH), 7.35–7.43 (m, 6 H, ArH, C=CH), 6.94 (d, *J* = 8.9 Hz, 2 H, ArH), 4.39 (t, *J* = 5.7 Hz, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 3.31 (t, *J* = 5.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 165.5, 158.8, 143.8, 135.3, 135.2, 132.0, 131.5, 130.3, 129.9, 129.6, 128.8, 128.2, 121.7, 117.3, 114.3, 68.8, 55.5, 36.5 ppm. IR: ṽ = 1686, 1647, 1611 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{23}BrNO_4$ [M + H]$^+$ 480.0810; found 480.0813.

(*E*)-*N*-(*p*-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropoxy)-3-(*p*-tolyl)-acrylamide (5i): This compound was obtained in 67% yield (278 mg); m.p. 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2 H, ArH), 7.74 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.58 (t, *J* = 7.4 Hz, 1 H, ArH), 7.42–7.55 (m, 6 H, ArH, C=CH), 7.19 (d, *J* = 7.7 Hz, 2 H, ArH), 6.94 (d, *J* = 8.9 Hz, 2 H, ArH), 4.40 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.36 (t, *J* = 5.8 Hz, 2 H, CH_2), 2.38 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 165.7, 158.6, 143.8, 140.1, 136.6, 133.5, 132.5, 131.7, 129.5, 129.5, 128.7, 128.3, 128.1, 126.1, 116.2, 114.3, 69.0, 55.6, 36.6, 21.5 ppm. IR: ṽ = 1681, 1655, 1615 cm^{-1}. MS (ESI): *m*/*z* = 438 [M + Na]$^+$. $C_{26}H_{25}NO_4$ (415.49): calcd. C 75.16, H 6.06, N 3.37; found C 74.91, H 5.71, N 3.16.

(*E*)-*N*-Hydroxy-*N*-(*p*-methoxyphenyl)-3-(*p*-tolyl)acrylamide (6i): This compound was obtained in 24% yield (68 mg); m.p. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.29 (d, *J* = 8.6 Hz, 2 H, ArH), 7.22 (d, *J* = 7.9 Hz, 2 H, ArH), 7.06 (d, *J* = 7.9 Hz, 2 H, ArH), 6.91 (d, *J* = 8.8 Hz, 2 H, ArH), 6.31 (d, *J* = 15.3 Hz, 1 H, C=CH), 3.80 (s, 3 H, OCH_3), 2.27 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 160.1, 142.6, 140.3, 132.0, 130.3, 129.5, 128.6, 127.9, 114.6, 114.0, 55.6, 21.4 ppm. IR: ṽ = 3117, 1636, 1592 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{18}NO_3$ [M + H]$^+$ 284.1287; found 284.1289.

(*E*)-*N*,3-Bis(*p*-methoxyphenyl)-*N*-(3-oxo-3-phenylpropoxy)acrylamide (5j): This compound was obtained in 64% yield (276 mg); m.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.4 Hz, 2 H, ArH), 7.72 (d, *J* = 15.7 Hz, 1 H, HC=C), 7.58 (t, *J* = 7.4 Hz, 1 H, ArH), 7.55 (br, 2 H, ArH), 7.42–7.49 (m, 4 H, ArH), 6.93 (d, *J* = 9.0 Hz, 2 H, ArH), 6.87–6.91 (m, 3 H, ArH, C=CH), 4.39 (t, *J* = 5.8 Hz, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.35 (t, *J* = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 161.1, 158.6, 143.5, 136.6, 133.5, 131.8, 129.9, 129.5, 128.7, 128.1, 128.0, 126.1, 121.6, 118.9, 114.8, 114.2, 68.9, 55.5, 55.4, 36.6 ppm. IR: ṽ = 1688, 1651, 1601 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{26}NO_5$ [M + H]$^+$ 432.1811; found 432.1819.

(*E*)-*N*-Hydroxy-*N*,3-bis(*p*-methoxyphenyl)acrylamide (6j): This compound was obtained in 17% yield (51 mg); m.p. 166–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.36 (d, *J* = 8.6 Hz, 2 H, ArH), 7.35 (d, *J* = 8.6 Hz, 2 H, ArH), 6.98 (d, *J* = 8.8 Hz, 2 H, ArH), 6.84 (d, *J* = 8.8 Hz, 2 H, ArH), 6.30 (d, *J* = 14.7 Hz, 1 H, C=CH), 3.87 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 161.1, 160.1, 142.3, 130.2, 129.6, 128.6, 127.5, 114.6, 114.2, 112.4, 55.6, 55.4 ppm. IR: ṽ = 3114, 1640, 1589, 1568 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{18}NO_4$ [M + H]$^+$ 300.1236; found 300.1234.

(*E*)-3-(4-Bromophenyl)-*N*-(*p*-methoxyphenyl)-*N*-(3-oxo-3-phenylpropoxy)acrylamide (5k): This compound was obtained in 71% yield (348 mg); m.p. 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.7 Hz, 2 H, ArH), 7.69 (d, *J* = 15.0 Hz, 1 H, HC=C), 7.59 (t, *J* = 7.2 Hz, 1 H, ArH), 7.43–7.52 (m, 8 H, ArH, C=CH), 6.94 (d, *J* = 7.9 Hz, 2 H, ArH), 4.39 (brs, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 3.34 (brs, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 158.7, 142.4, 136.5, 134.2, 133.6, 132.0, 131.4, 129.7, 128.7, 128.1, 125.7, 124.0, 118.1, 114.3, 68.8, 55.6, 36.5 ppm. IR: ṽ = 1677, 1655, 1616 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{23}BrNO_4$ [M + H]$^+$ 480.0810; found 480.0811.

(*E*)-3-(*p*-Bromophenyl)-*N*-hydroxy-*N*-(*p*-methoxyphenyl)acrylamide (6k): This compound was obtained in 15% yield (54 mg); m.p. 167–168 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.81 (brs, 1 H, OH), 7.40–7.70 (m, 8 H, ArH, CH=CH), 6.97 (d, *J* = 8.9 Hz, 2 H, ArH), 3.77 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 164.0, 156.8, 140.3, 134.7, 134.1, 131.9, 129.8, 123.0, 120.7, 119.3, 113.6, 55.3 ppm. IR: ṽ = 3114, 1641, 1587, 1573 cm^{-1}. HRMS (ESI): calcd. for $C_{1.6}H_{15}BrNO_3$ [M + H]$^+$ 348.0235; found 348.0231.

(*E*)-*N*-(*p*-Methoxyphenyl)-3-(*p*-nitrophenyl)-*N*-(3-oxo-3-phenylpropoxy)acrylamide (5l): This compound was obtained in 63% yield (294 mg); m.p. 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.8 Hz, 2 H, ArH), 7.99 (d, *J* = 7.2 Hz, 2 H, ArH), 7.82 (brs, 2 H, ArH), 7.77 (d, *J* = 15.9 Hz, 1 H, HC=C), 7.60 (t, *J* = 7.4 Hz, 1 H, ArH), 7.44–7.52 (m, 5 H, ArH, C=CH), 6.96 (d, *J* = 9.0 Hz, 2 H, ArH), 4.41 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.34 (t, *J* = 5.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 165.0, 158.5, 148.1, 141.6, 140.8, 136.4, 133.8, 131.0, 128.9, 128.8, 128.1, 125.3, 124.0, 122.0, 114.3, 68.7, 55.5, 36.3 ppm. IR: ṽ = 1681, 1651, 1616, 1509 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{23}N_2O_6$ [M + H]$^+$ 447.1556; found 447.1567.

(*E*)-*N*-Hydroxy-*N*-(*p*-methoxyphenyl)-3-(*p*-nitrophenyl)acrylamide (6l): This compound was obtained in 18% yield (60 mg); m.p. 185–186 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.93 (brs, 1 H, OH), 8.25 (d, *J* = 7.8 Hz, 2 H, ArH), 7.99 (brs, 2 H, ArH), 7.72 (d, *J* = 15.6 Hz, 1 H, HC=C), 7.59 (brs, 3 H, ArH, C=CH), 6.99 (d, *J* = 8.6 Hz, 2 H, ArH), 3.78 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 163.5, 156.8, 147.6, 141.4, 139.1, 134.5, 129.0, 124.0, 122.8, 120.7, 113.7, 55.3 ppm. IR: ṽ = 3196, 1642, 1602, 1594, 1522, 1509 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{15}N_2O_5$ [M + H]$^+$ 315.0981; found 315.0974.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H NMR and ^{13}C NMR spectra of products **5** and **6**, excluding those byproducts without full characterization.

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[1] a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655 and reference therein b) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000 and reference therein.
[2] D. Seebach, *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[3] a) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki, T. Sakai, *Org. Lett.* **2009**, *11*, 4866–4869; b) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630; c) D. Enders, A. Henseler, *Adv. Synth. Catal.* **2009**, *351*, 1749–1752; d) D. Enders, A. Grossmann, J. Fronert, G. Raabe, *Chem. Commun.* **2010**, *46*, 6282–6284; e) Y. Shimakawa, T. Morikawa, S. Sakaguchi, *Tetrahedron Lett.* **2010**, *51*, 1786–1789.
[4] a) D. A. DiRocco, K. M. Oberg, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10872–10874; b) Y. Li, F.-Q. Shi, Q.-L. He, S.-L. You, *Org. Lett.* **2009**, *11*, 3182–3185; c) Q. Liu, T. Rovis, *Org. Lett.* **2009**, *11*, 2856–2859; d) J. Read de Alaniz, T. Rovis, *Synlett* **2009**, 1189–1207; e) Q. Liu, S. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14066–14067.
[5] a) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; c) C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418.
[6] a) M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131; b) M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266–17267.
[7] a) J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2009**, *11*, 677–680; b) V. Nair, B. P. Babu, S. Vellalath, V. Varghese, A. E. Raveendran, E. Suresh, *Org. Lett.* **2009**, *11*, 2507–2510; c) V. Nair, B. P. Babu, S. Vellalath, E. Suresh, *Chem. Commun.* **2008**, 747–749.
[8] a) V. Nair, V. Sreekumar, S. Bindu, E. Suresh, *Org. Lett.* **2005**, *7*, 2297–2300; b) V. Nair, S. Bindu, V. Sreekumar, A. Chiaroni, *Org. Lett.* **2002**, *4*, 2821; c) V. Nair, S. Bindu, V. Sreekumar, N. P. Rath, *Org. Lett.* **2003**, *5*, 665–667; d) C. Ma, H. Ding, G. Wu, Y. Yang, *J. Org. Chem.* **2005**, *70*, 8919–8923; e) C. Ma, Y. Yang, *Org. Lett.* **2005**, *7*, 1343–1345; f) C. Ma, H. Ding, Y. Zhang, M. Bian, *Angew. Chem.* **2006**, *118*, 7957; *Angew. Chem. Int. Ed.* **2006**, *45*, 7793–7797; g) H. Ding, Y. Zhang, M. Bian, W. Yao, C. Ma, *J. Org. Chem.* **2008**, *73*, 578–584; h) H.-R. Pan, X.-R. Wang, C.-X. Yan, Z.-X. Sun, Y. Cheng, *Org. Biomol. Chem.* **2011**, *9*, 2166–2174; i) H.-R. Pan, Y.-J. Li, C.-X. Yan, J. Xing, Y. Cheng, *J. Org. Chem.* **2010**, *75*, 6644–6652.
[9] a) J. Ma, Y. Huang, R. Chen, *Org. Biomol. Chem.* **2011**, *9*, 1791–1798; b) D. Du, Z. Hu, J. Jin, Y. Lu, W. Tang, B. Wang, T. Lu, *Org. Lett.* **2012**, *14*, 1274–1277.
[10] a) F. T. Wong, P. K. Patra, J. Seayad, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 2333–2336; b) Z.-X. Sun, Y. Cheng, *Org. Biomol. Chem.* **2012**, *10*, 4088–4094.
[11] a) W. Yao, M. Bian, G. Wang, C. Ma, *Synthesis* **2011**, 1998–2002; b) L. Yang, B. Tan, F. Wang, G. Zhong, *J. Org. Chem.* **2009**, *74*, 1744–1746; c) J. Seayad, P. K. Patra, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 953–956.
[12] T. Wang, X.-L. Huang, S. Ye, *Org. Biomol. Chem.* **2010**, *8*, 5007–5011.
[13] a) N. Shao, G.-X. Pang, C.-X. Yan, G.-F. Shi, Y. Cheng, *J. Org. Chem.* **2011**, *76*, 7458–7465; b) J. Xing, X.-R. Wang, C.-X. Yan, Y. Cheng, *J. Org. Chem.* **2011**, *76*, 4746–4752; c) Y. Cheng, Y.-G. Ma, X.-R. Wang, J.-M. Mo, *J. Org. Chem.* **2009**, *74*, 850–855; d) Y. Cheng, B. Wang, X.-R. Wang, J.-H. Zhang, D.-C. Fang, *J. Org. Chem.* **2009**, *74*, 2357–2367; e) J.-Q. Li, R.-Z. Liao, W.-J. Ding, Y. Cheng, *J. Org. Chem.* **2007**, *72*, 6266–6269; f) Y. Cheng, M.-F. Liu, D.-C. Fang, X.-M. Lei, *Chem. Eur. J.* **2007**, *13*, 4282–4292; g) M.-F. Liu, B. Wang, Y. Cheng, *Chem. Commun.* **2006**, 1215–1217.
[14] Y. Cheng, J.-H. Peng, Y.-J. Li, X.-Y. Shi, M.-S. Tang, T.-Y. Tan, *J. Org. Chem.* **2011**, *76*, 1844–1851.
[15] CCDC-864843 (for **5i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[16] E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179–13181.
[17] J. L. Belletire, R. A. Bills, S. A. Shackelford, *Synth. Commun.* **2008**, *38*, 738–745.
[18] J. Z. Vlahakis, C. Lazar, I. E. Crandall, W. A. Szarek, *Bioorg. Med. Chem.* **2010**, *18*, 6184–6196.
[19] J. E. Thomson, C. D. Campbell, C. Concellon, N. Duguet, K. Rix, A. M. Z. Slawin, A. D. Smith, *J. Org. Chem.* **2008**, *73*, 2784–2791.
[20] T. D. Avery, D. Caiazza, J. A. Culbert, D. K. Taylor, E. R. T. Tiekink, *J. Org. Chem.* **2005**, *70*, 8344–8351.
[21] A. Defoin, *Synthesis* **2004**, 706–710.
[22] a) X.-L. An, J.-R. Chen, C.-F. Li, F.-G. Zhang, Y.-Q. Zou, Y.-C. Guo, W.-J. Xiao, *Chem. Asian J.* **2010**, *5*, 2258–2265; b) K. Miyauchi, K. Hori, T. Hirai, M. Takebayashi, T. Ibata, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2142–2146.

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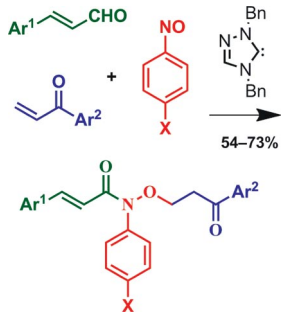
NHC-catalyzed three-component reactions of α,β-unsaturated aldehydes (enals), nitrosoarenes, and α,β-unsaturated ketones (enones) proceeded through a cascade aza-benzoin condensation/oxo-Michael addition sequence to produce *N*,*O*-bisfunctionalized *N*-hydroxylacrylamides in moderate to good yields.



Keywords: Synthetic methods / Multicomponent reactions / Domino reactions / Cascade reactions / Carbenes / Enones / Enals / Nitrosoarenes

