JOC Article

Multiple Component Reactions: An Efficient Nickel-Catalyzed Reformatsky-Type Reaction and Its Application in the Parallel Synthesis of β-Amino Carbonyl Libraries

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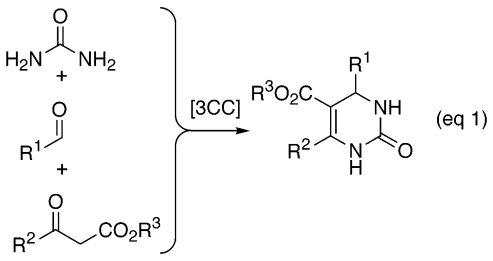
Multiple-component condensations (MCC) where three or more reactants combine to afford a new core structure possessing the molecular features of its composite building blocks is a powerful method for the preparation of molecular diversity. We have developed an efficient, nickel-catalyzed, Reformatsky-type three-component condensation (3CC) reaction that affords β-amino carbonyl compounds. The scope of the reaction is demonstrated both in the gram and microscale settings; 15 β-amino esters, amides, and a ketone were prepared efficiently at the mmol scale, and a library of 64 β-amino carbonyl compounds was generated at the μmol scale.

Introduction

The classic paradigm for drug discovery involves the iterative screening of potential drug candidates against biological targets, followed by the sequential optimization of lead compounds through systematic modifications to the core structure. The advent of high-throughput biological assays and the ability to evaluate large numbers of compounds in parallel, however, has placed a severe strain on this iterative approach. A complementary strategy and recognized solution to the synthetic limitations of the classical strategy is the use of multiple-component condensations (MCC) to provide the requisite small molecule diversity more efficiently.[1] Many unique structures can be afforded rapidly when three or more reactants are combined in a single step to afford new compounds possessing the combined features of the building blocks. One of many examples of a three-component condensation (3CC), the Biginelli reaction, brings together ureas, aldehydes and β-ketoesters, to afford functionalized pyrimidinones as the core structure (eq1).[2] The combinatorial nature of this reaction allows for the preparation of numerous compounds from a relatively few building blocks. In this regard, the MCC strategy can be a valuable tool for the preparation of large libraries of compounds based on a common core structure whose diversity will be proportional to the number and availability of inputs.

Since its discovery over 115 years ago, the Reformatsky reaction has found wide use in synthesis[3,4] due, in part,



to the high functional group tolerance of organozinc reagents.[5] Reformatsky reagents are prepared easily, usually in situ, by the reaction of an α-halo ester with some form of activated zinc metal. The position of the halogen determines precisely the site of zinc insertion allowing for regioselective enolate formation in polycarbonyl compounds.[4] The activated zinc reagents, however, must be prepared fresh, and often the generation of the most active metals can be laborious. In light of these issues, it is surprising that little attention has been placed on developing a catalytic version of the classic Reformatsky reaction.

About 10 years ago, Périchon and co-workers published a series of articles where they disclosed a new electrochemical Reformatsky reaction in which they reported that the yields of the β-hydroxy ester products were markedly increased by the addition of sub-stoichiometric amounts of $Ni(II)Br_2$(2,2′-bipyridine).[6]

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(1) (a) Armstrong, W. R.; Combs, A. P.; Tempest, P. A.; Brown, D. B.; Keating, T. A. *Acc. Chem. Res.* **1996,** *29*, 123−131. For leading references, see: (b) Kobayashi, S. *Curr. Opin. Chem. Biol.* **2000,** *4*, 338−345. (c) Willi, B. *Methods Princ. Med. Chem.* **2000,** *9*, 6−21.

(2) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962.

(3) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210.

(4) For recent reviews of the Reformatsky reaction, see: (a) Fürstner, A. *Synthesis* **1989**, 571−590. (b) Rathke M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 277−299. (c) Fürstner, A In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; pp 287−305.

(5) (a) Inoue, S.; Imanaka, Y. *J. Organomet. Chem.* **1972**, *35*, 1−7. For leading references, see: (b) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 3. 2117−2188. (c) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414−4435.

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In 1992, Ding and Zhao reported that the reaction of ethyl bromoacetate (and propanoate) with various aldehydes and ketones in the presence of zinc dust and catalytic amounts of Cp_2TiCl_2 afforded cleanly the classic Reformatsky β-hydroxy ester products in good to excellent yields.[7] However, the authors propose that the active nucleophile is actually a titanium enolate. This hypothesis is supported by the observation that only 0.5 equiv of zinc metal is required to achieve high levels of conversion.

Recently, Honda and colleagues reported a rhodium-catalyzed Reformatsky-type reaction in which diethylzinc acted as the zinc source.[8] While the overall yields of the β-hydroxy esters for this transformation were modest, the development of this type of catalytic system represents a significant advancement in the Reformatsky reaction.

Similarly, Dolbier and co-workers reported that the reaction of ethyl bromofluoroacetate with several aldehydes and ketones in the presence of zinc dust and a catalytic amount of $CeCl_3 \cdot 7H_2O$ afforded a limited number of α-fluoro-β-hydroxy ester products in good to excellent yields.[9]

That imines can be substituted for the classic Reformatsky partners, aldehydes or ketones, was first disclosed by Gilman and Speeter nearly 60 year ago.[10] However, this transformation can be problematic, often affording a mixture of β-amino esters and β-lactams.[11] Recently, we have shown that imines prepared from 2-methoxyaniline, such as **1**, afford the β-amino esters as the sole products.[12]

Despite the high functional group tolerance of the Reformatsky reagent and convenience of in situ generation of the nucleophile and imine, there remains a surprising dearth of MCC examples; we are aware of only three.[13] In all cases, the yields have been modest and required the use of a potentially explosive reagent[13b] or a fairly expensive catalyst.[13c] To date, none of these methods demonstrate sufficient synthetic efficiency to be applied effectively to the preparation of a combinatorial library of Reformatsky products.

We wish to disclose our results in this area: the development of an efficient, nickel-catalyzed Reformatsky-type three-component condensation that combines an aldehyde, aniline, and an α-bromocarbonyl to afford compounds with a β-amino carbonyl core structure.[14]

SCHEME 1

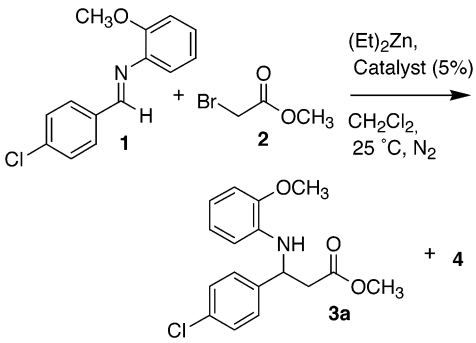


TABLE 1. Comparison of Catalytic Activity

entry	catalyst[a]	ester[b] **3a** (%)	ethyl adduct[b] **4** (%)	convn[b] (%)	time[c] (h)
1	$RhCl(PPh_3)_3$	98	2	100	2.0
2	$Pd(dba)_2$	71	29	100	0.5
3	$PdCl_2(PPh_3)_2$	61	39	100	0.5
4	$Ni(acac)_2$[d]	>95	<5	100	0.5
5	$Ni(acac)_2$[e]	99	1	100	0.5
6	$NiCl_2(PPh_3)_2$	99	1	100	0.5
7	$Cr(acac)_3$	50	50	80	2.0
8	$Cr(acac)_3$[e]	50	50	100	2.0
9	$Fe(acac)_2$	60	40	60	24
10	$Fe(acac)_2$[e]	55	45	95	24
11	$Co(acac)_3$	55	45	100	2.0
12	$Co(acac)_3$[e]	45	55	100	2.0
13	$Cr(CH_3O_2)_2$	<1	>99	≈20	24
14	$Fe(CO)_5$	<1	>99	≈20	24
15	$Cu(CF_3SO_3)_2$	<1	>99	≈20	24
16	$ZrCp_2Cl_2$	<1	>99	≈20	24

[a] Catalyst loading: 5 mol %. [b] Based on ^1H NMR analysis of reaction mixtures directly after workup. [c] Time of reaction quench, based on TLC determination of conversion or after 24 h. [d] After 5 min, a black precipitate, presumably nickel metal, was observed. [e] 10 mol % of PPh_3 was added to the reaction as a co-ligand.

Herein, we demonstrate the scope of this new nickel-catalyzed process at both macro- and microscales. We prepared 15 compounds at the mmol scale with typical yields of ≥90%, and we conducted a parallel synthesis of a library consisting of 64 β-amino carbonyl compounds at a μmole scale.

Results and Discussion

Catalyst Activity. Our primary objective was to improve the efficiency and expand the scope and utility of the Reformatsky-type addition of ester, amide, and ketone enolates to imines.[4] Our previous experience also indicated that Reformatsky additions to imines were significantly more facile when conducted in CH_2Cl_2.[12] Thus, we began our efforts to improve further the transformation by establishing a metal-catalyzed reaction of imine **1** and methyl bromoacetate (**2**) (Scheme 1). In this regard, a catalytic Reformatsky reaction using Wilkinson's catalyst and diethylzinc in CH_2Cl_2 afforded the β-amino ester **3a** (Table 1, entry 1). The initial success was encouraging, but three observations gave us pause. First, the color of the product was nearly black and required several purification cycles (in this case, recrystallization), which afforded, at best, a gray crystalline material and resulted in a significant reduction in the isolated yield (61% from crude yield of 96%). Second, while Honda and co-workers did not report the formation

(6) (a) Sibille, S.; d'Incam, E.; Leport, L.; Massebiau, M.-C.; Périchon J. *Tetrahedron Lett.* **1987**, *28*, 55−58. (b) Mcharek, S.; Sibille, S.; Nédélec, J.-Y.; Périchon J. *J. Organomet. Chem.* **1991**, *401*, 211−215. (c) Conan, A.; Sibille, S.; Périchon J. *J. Org, Chem.* **1991**, *56*, 2018−2024.

(7) Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941−942.

(8) Kanai, K.; Wakabayashi, H.; Honda, T *Org. Lett.* **2000**, *2*, 2549−2551.

(9) Ocampo, R.; Dolbier, W. R.; Abboud, K. A.; Zuluaga, F. *J. Org. Chem.* **2002,** *67*, 72−78.

(10) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943,** *65*, 2255−2256.

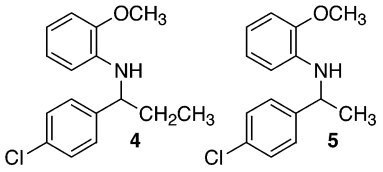
(11) Dardoize and co-workers reported that β-amino esters and lactams were formed in ratios that were temperature dependent. For leading references, see: Dardoize, F.; Moreau, J.-L.; Gaudemar, M *Bull. Soc. Chim. Fr.* **1972,** 3841−3846.

(12) Adrian, J. C., Jr.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457−2460.

(13) (a) Nishiyama, T.; Kishi, H.; Kitano, K.; Yamada, F. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1765−1768. (b) Saidi, M. R.; Azizi, N.; Zali-Boinee, H. *Tetrahedron* **2001**, *57*, 6829−6832. (c) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307−308.

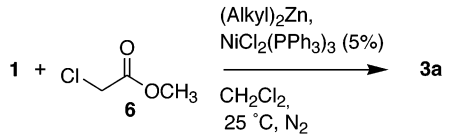
of an ethyl adduct, we observed the ethyl adduct **4** as a minor component (2%).[15] This difference in reactivity may be due to differences in reaction times. Honda and co-workers quench their reactions with carbonyl electrophiles after about 5 min[8] and with in situ generated imines after about 10 min.[13c,16] In contrast, our imine required 2 h to achieve 100% conversion as determined by TLC analysis.[17] Third, and perhaps most significantly, was the relatively high cost of Wilkinson's catalyst.

Given these above-mentioned concerns, we decided to evaluate other metal salts for potential catalytic activity in this reaction system. The results of this study are presented in Table 1; it is clear from these data that several metals catalyze the transformation. We focused our attention on those salts that afforded 100% conversion in the shortest time (i.e., Pd and Ni salts). The two palladium catalysts, $Pd(dba)_2$ and $PdCl_2(PPh_3)_3$ (entries 2 and 3), both lead to complete conversion within 30 min; however, despite attempts at further optimization, these catalysts also generated a significant fraction of the undesired ethyl adduct **4**.



Consistent with the observations of Périchon and co-workers, the nickel catalysts (entries 4−6) were extremely active,[6c] affording the *β*-amino ester **3a** as the major product in all cases. Initially, we found that while $Ni^{II}(acac)_2$ alone (entry 4) was an effective catalyst, the reaction was beset by two problems. First, as the reaction proceeded, a black precipitate was formed that appeared to carry through to the product infecting it with a dark impurity, similar to that observed with Wilkinson's catalyst. The second problem was the formation of the ethyl adduct **4**, while less than that observed with the palladium catalysts by a factor of 6, it still represented a significant fraction of the product mixture. We reasoned that the black precipitate observed during the reaction was metallic nickel that had been reduced as a result of the catalytic process and that this might be countered by the addition of a stabilizing ligand to the reaction mixture. To our satisfaction, the addition of 2 equiv (relative to catalyst loading, entry 5) of PPh_3 to the reaction mixture nearly eliminated the precipitation problem. A pleasant surprise was that the inclusion of the co-ligand also reduced significantly the formation of **4**. For practical considerations, we decided to try $Ni^{II}Cl_2(PPh_3)_2$ (entry 6). We were delighted to find that it was extremely active, there was no appreciable black contaminate, and most important, the ethyl adduct **4** was barely detectable by ^1H NMR.

SCHEME 2



Alkyl	% Conv.	% **3a**	% Alkyl adduct	Time(h)
Ethyl	100	94	≤ 5	1.5
Methyl	0	0	0	1.5

To shift further the unavoidable competition between the two in situ nucleophiles, the zinc enolate and the alkyl zinc, in favor of the addition of the zinc enolate, we switched from diethylzinc to the considerably less nucleophilic dimethylzinc.[5] While for the most part this was a cosmetic change, it turned out to be not without consequence. Since this reaction worked well with the methyl bromoacetate **2**, we were curious to see if it was equally reactive with the methyl chloroacetate **6**. For example, Périchon and co-workers conducted their nickel-catalyzed electrochemical Reformatsky reactions with α-chloro esters or nitriles.[6] The results of this experiment are presented in Scheme 2. The methyl chloroacetate proved to be active only when diethylzinc was used as the zinc source and was completely inert when dimethylzinc was used. It is important to note that while no Reformatsky adduct was formed when dimethylzinc was used, within the time frame of the experiment (vida infra) no methyl adduct **5** was detected either.

With these results in hand, we next turned our attention to the effect of catalyst loading of the reaction of imine **1** with methyl bromoacetate **2**. The results of these experiments are presented in Table 2. These data indicate that optimum catalyst loading for this process is 4−5 mol %. At this level of catalyst loading, there is no detectable methyl adduct **5** formed. It is not surprising that as the catalyst loading decreases there is a concomitant increase in the ratio of methyl adduct and the time required to achieve 100% conversion. Note that at zero catalyst loading, the reaction (by this we mean the formation of methyl adduct) attains only 80% conversion within 3 days, thus confirming the importance of the nickel catalyst.

On the basis of a detailed electrochemical study by Périchon et al.[6c] and a complimentary mechanistic study by Heathcock and co-workers on ethylzinc enolate formation from an α-bromo ketone and diethylzinc, a reasonable mechanistic picture emerges (Scheme 3). The catalytic cycle is initiated by the in situ generation of the active Ni(0), which then adds oxidatively into the α-halo carbonyl. After formation of the initial Ni(II) complex, ligand exchange with the dimethylzinc affords a halozinc enolate (or methylzinc enolate) and a second Ni(II) complex. The zinc enolate goes on to react with the imine, generated in situ (vida infra) or not, which upon hydrolysis gives the *β*-amino carbonyl. The second Ni(II) complex undergoes a reductive elimination to return the active Ni(0) catalyst.

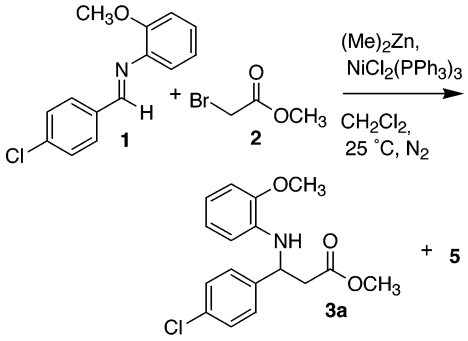
(14) The *β*-amino carbonyl products of the multicomponent Reformatsky method reported herein are complimentary to those obtained from the Mannich reaction. For recent examples of multicomponent Mannich reactions, see: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (b) Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 3227−3237. (c) Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577−1579. (d) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426−1428.

(15) Based on the relative integration in the ^1H NMR of the reaction mixture after workup.

(16) In their initial paper (ref 8), Honda and co-workers specifically comment that no ethyl adducts were observed. In their subsequent paper (ref 13c), they make no comment on the formation of ethyl adducts.

(17) In this initial case and in all subsequent cases, the reactions were judged to be complete based on the disappearance of the limiting aldehyde as determined by TLC. We made no attempt to determine the relative rate of formation of the ester **3a** beyond following the course of the reaction by TLC.

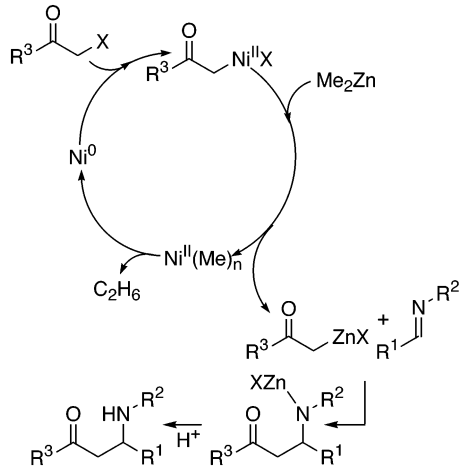
TABLE 2. Effect of Catalyst Loading[a]



entry	catalyst loading (%)	ester **3a**[b] (%)	methyl adduct **5**[b] (%)	time (h)
1	0.0	0	80[c]	72
2	0.1	48	52	40
3	0.5	72	28	16
4	1.0	88	12	16
5	2.0	94	6	4
6	3.0	99	1	2
7	4.0	≥99	≤1[d]	2
8	5.0	≥99	≤1[d]	1.5

[a] Unless otherwise noted, all reactions reached 100% conversion as determined by TLC. [b] Determined by ^{1}H NMR of the reaction mixture directly after workup. [c] Only 80% conversion at quench. [d] Undetectable in the ^{1}H NMR of the reaction mixture directly after workup.

SCHEME 3. Proposed Catalytic Cycle



Nickel-Catalyzed Reformatsky 3CC. At this point, we initiated our effort to improve the efficiency further by converting this reaction to a multicomponent process (Table 3). In our preliminary experiments, we combined all reagents used in entry 1 of Table 3, less the catalyst. After allowing time for imine formation, approximately 30 min, a solution of the Ni(II) catalyst was added. While these experiments afforded the desired β-amino ester **3a**, yields never exceeded 60% and the crude product mixtures were troubled with impurities. These results suggested that the order of addition might be important.

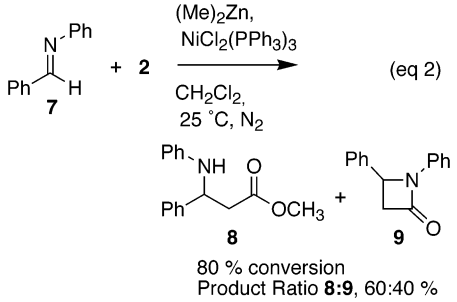
We reasoned that the imine should be prepared first, followed by addition of the bromo compound and catalyst. To test this hypothesis, we stirred the 4-chlorobenzaldehyde (1 equiv) together with the 2-methoxyaniline (1.02 equiv) in CH_2Cl_2. After 30 min, a toluene solution of the dimethylzinc (3.5 equiv) was added, which served the dual role as both the zinc source and dehydrating agent. After an additional 15 min, methyl 2-bromoacetate (1.05 equiv) was added followed immediately by a CH_2Cl_2 solution of the catalyst. The reaction was followed by TLC and reached 100% conversion within 1.5 h. This order of addition afforded the desired β-amino ester **3a** in a 96% yield (entry 1). To our delight, the purity of the crude product, as determined by ^{1}H NMR, was also excellent.

Flushed with success, we explored the scope of this novel MCC protocol, and the results are presented in Table 3. In all but one case (entry 13), the isolated yields are greater than 80%, and in virtually all cases the product purity out of the reaction workup was sufficient for preparative purposes without further purification.

We looked initially at the α-bromocarbonyl component (entries 1−5) and found that esters (entry 1), *tert*-butyl ketone (entry 2), and various tertiary amides[18] (entries 3−5) were all active participants in the reaction. The 1-bromo-3,3-dimethyl-2-butanone (entry 2) was found to be the only active ketone. Attempts with the commercially available 2-bromoacetophenone resulted in low yields of the β-amino ketone. Presumably, this is due to the undesired reaction of the acetophenone carbonyl with the enolate.[6c,8] This disadvantage is mitigated, however, by the fact that the Weinreb amide (entry 3) was found to be an active reaction partner, thus affording access to a wide array of β-amino ketones as well as aldehydes.[19,20]

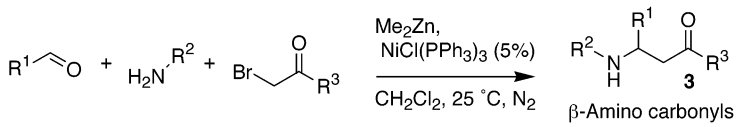
All 2-methoxyaniline derivatives tested (all entries except 7 and 8) were sufficiently activating and afforded either the β-amino ester or amide. We also found that the 2-(*N*,*N*-dimethylamino)aniline (entry 7) and 2-amino-6-methylpyridine (entry 8) were equally reactive, giving the β-amino esters as the only observed products in both cases.

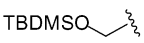
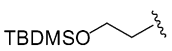
The need for an electronegative group in the ortho position was clearly demonstrated in the reaction with imine **7** derived from benzaldehyde and aniline (eq 2). Imine **7** lacks an electronegative group in the ortho position and reacted sluggishly, achieving only an 80% conversion after 10 h as well as affording a mixture of the ester **8** and lactam **9**.[21,22] This observation is consistent with our previous observation that imines derived from 2-methoxyaniline afford the β-amino esters as the sole products under more traditional Reformatsky conditions.[12]



All aldehydes tested, both enolizable (entries 11, 14, and 15) and nonenolizable (all other entries of Table 3) were found to be active. The reaction appears to be sensitive to steric demand at the α-position, as evidenced by the significantly lower yield of 2,2-dimethylpropanal (entry 13). This is particularly apparent when the yields of the two TBDMS-protected hydroxyaldehydes, 2-hy-

TABLE 3. 3CC Nickel-Catalyzed Reformatsky Reaction Affording Compounds with the β-Amino Carbonyl Core Structure[a]



Entry	Adduct	R^1	R^2	R^3	Yield (%)[b] (% Purity[c])
1	**3a**	p-ClPh	2-MeOPh	OMe	96 (≥ 96)
2	**3b**	*p*-ClPh	2-MeOPh	*Tert*-Bu	96 (≥ 96)
3	**3c**	*p*-ClPh	2-MeOPh	$NCH_3(OCH_3)$	86 (≥ 90)
4	**3d**	*p*-ClPh	2-MeOPh	$N(CH_3)_2$	95 (≥ 95)
5	**3e**	*p*-ClPh	2-MeOPh		94 (≥ 95)
6	**3f**	*p*-ClPh	2-MeO-5-MePh	OMe	96 (≥ 96)
7	**3g**	*p*-ClPh	2-Me_2NPh	OMe	97 (≥ 97)
8	**3h**	*p*-ClPh		OMe	95 (≥ 95)
9	**3i**		2,4-DiMeOPh	OMe	95 (≥ 90)
10	**3j**		2-MeOPh	OMe	96 (≥ 96)
11	**3k**		2-MeOPh	OMe	81 (≥ 90)
12	**3l**		2-MeOPh	OMe	97 (≥ 97)
13	**3m**		2-MeOPh	OMe	58 (70)
14	**3n**		2-MeOPh	OMe	96 (≥ 96)
15	**3o**		2-MeOPh	OMe	87 (≥ 90)

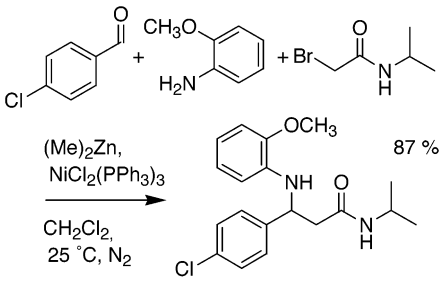
[a] All reactions were run on a 1 mmol scale in which the aldehyde was the limiting reagent. Typical molar ratios of starting materials: aldehyde/aniline/bromocarbonyl 1:1.02:1.05. [b] Isolated. [c] Determined from ^{1}H NMR of the reaction mixture immediately after workup.

droxyethanal (entry 11, 81%) and 3-hydroxypropanal (entry 14, 96%), are compared with that of 2,2-dimethylpropanal (58%).

Chemical Library. In light of the high efficiency achieved, the Ni-catalyzed 3CC Reformatsky reaction is ideally suited for the parallel synthesis of a combinatorial library of compounds based on the β-amino carbonyl core structure. Using a 96-well microtiter plate, a small library consisting of 64 members (4 aldehydes × 4 α-bromocarbonyls × 4 anilines) was prepared and distributed such that one product was formed per well (Figure 1). Inputs for this library were chosen from the building blocks used in Table 3, representing 54 novel combinations. Of the possible 64 compounds, 10 had been prepared previously on scale-up.

The array was conducted on a 25 μmol scale in which the aldehyde was the limiting reagent. An LCMS−UV analysis of the reaction wells indicated that in every case the major, if not only, product was the predicted β-aminocarbonyl compound. In all cases, the M + H signal observed was that of the expected molecular weight for

(18) We have since determined that secondary amides are also effective enolate sources. The following example has not been optimized:



(19) Nahm, S.; Weinreb, S. M.; *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(20) For reviews on the growing synthetic utility of the Weinreb amide, see: (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15−40. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340−347.

(21) The "activating" effect of an electron-withdrawing group at the ortho position of the *N*-phenyl group has also been observed for addition of lithium enolates to imines; see: Saito, S.; Hatanaka, K.; Yamaoto, H. *Org. Lett.* **2000,** *2*, 1891−1894.

(22) Ester and lactam ratio was based on the relative integration of the β-proton signal (lactam 5.01 ppm, ester 4.84 ppm) in the ^{1}H NMR of the reaction mixture after workup.

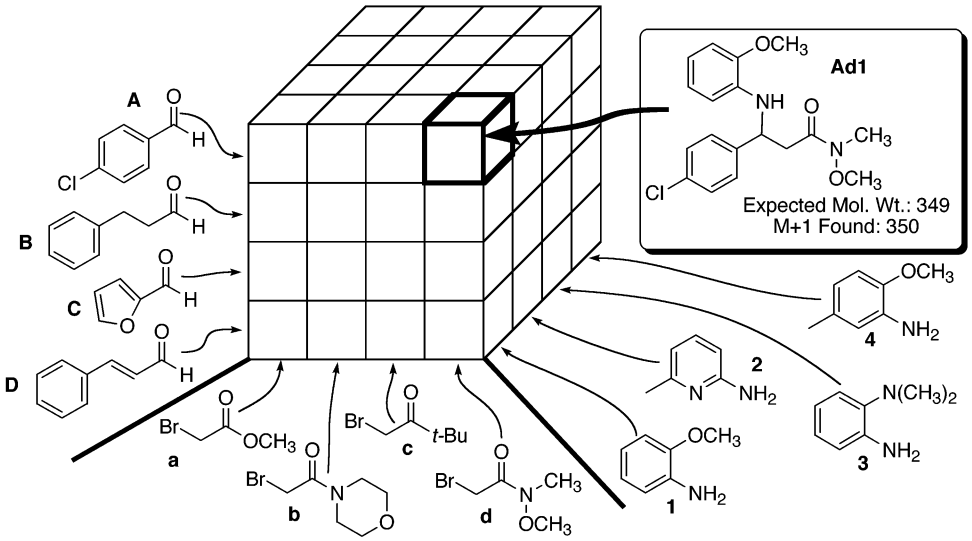


FIGURE 1. Chemical inputs for a three-dimensional three-component array and example positional decoding for the product structure **Ad1**.

the given components, and in a few cases, an M + Na signal was also observed.[23]

Summary

We have developed a highly efficient, nickel-catalyzed, Reformatsky-type three-component condensation reaction that affords β-amino carbonyl compounds as its core structure. This reaction uses an inexpensive nickel catalyst and is competent at both gram and microscale settings. In addition, we have demonstrated its utility in the parallel generation of molecular diversity by preparing a 64 β-amino carbonyl compound library. Given the large number of commercially available aldehydes, there is significant potential for preparing extremely large libraries. Adaptation of this reaction to the solid phase, as well as the development of other multicomponent condensation reactions, are underway and will be reported in due course.

Experimental Section

General Considerations. Melting points were measured in open capillary tubes and are uncorrected. Robertson Microlit Laboratories, Inc. of Madison, NJ performed the elemental analyses. The Mass Spectrometry Service of the University of Illinois performed the low- and high-resolution mass spectra. LCMS analysis was preformed by the Mass Spectrometry Service of Boston College. ^{1}H NMR spectra were determined at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz. Chemical shifts are expressed in parts per million (δ units) downfield from tetramethylsilane used as an internal reference. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2 immediately prior to use. All other commercially available reagents and solvents were used without further purification unless otherwise noted.

General Procedure. Methyl 3-(2-Methoxyphenyl)-amino-3-(4-chlorophenyl)propanoate (3a). To a stirred solution of 4-chlorobenzaldehyde (139 mg, 0.98 mmol) in CH_2Cl_2 (7.5 mL) at room temperature was added 2-methoxyaniline (115 μL, 1.02 mmol). After 30 min, a solution of dimethylzinc (1.75 mL, 2M, 3.5 mmol) in toluene was added all at once. After 15 min, the methyl bromoacetate (100 μL, 1.05 mmol) was added, followed immediately by a freshly prepared solution of bistriphenylphosphine nickel(II) dichloride (2.5 mL, 0.02M, 0.05 mmol) in CH_2Cl_2. The reaction progress was followed by TLC. However, unless otherwise noted, all reactions were quenched after 1−3 h by the addition of aqueous HCl (2.0 mL, 2 M). The organic phase was separated, washed sequentially with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to afford 302 mg (96%) of **3a** as a yellow-orange oil that crystallizes: mp = 84−85 °C; R_f = 0.11 (SiO_2, 40% hexane/CH_2Cl_2); IR (thin film) 3410.6, 1734.2 cm^{-1}; 300 MHz ^{1}H NMR δ 7.32 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz), 6.77 (dd, 1H, J = 9.0, 3.0 Hz), 6.71 (td, 1H, J = 9.0, 2.0 Hz), 6.45 (td, 1H, J = 9.0 Hz, 3.0 Hz), 6.36 (dd, 1H, J = 9.0, 2.0 Hz), 5.03 (d, 1H, J = 6.0 Hz), 4.82 (m, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 2.86 (dd, 1H, J = 15.0, 5.0 Hz), 2.79 (dd, 1H, J = 15.0, 4.0 Hz); 75 MHz ^{13}C NMR δ 171.1, 146.8, 140.8, 136.2, 132.9, 128.8, 127.6, 121.0, 117.1, 111.1, 109.4, 55.4, 54.0, 51.8, 42.7. Anal. Calcd for $C_{17}H_{18}ClNO_3$: C, 63.85; H, 5.67; N, 4.38. Found: C, 64.12; H, 5.54; N, 4.17.

1-(2-Methoxyphenyl)amino-1-(4-chlorophenyl)-3,3-dimethyl-3-pentanone (3b). Compound **3b** was isolated as a brown oil (96%): R_f = 0.42 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3415.9, 1702.3 cm^{-1}; 300 MHz ^{1}H NMR δ 7.31 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 6.77−6.60 (m, 4H), 6.37 (dd, 1H, J = 8.0, 2.0 Hz), 4.97 (s, 1H), 4.88 (m, 1H), 3.87 (s, 3H), 3.04 (dd, 1H, J = 17.0, 6.0 Hz), 2.95 (dd, 1H, J = 17.0, 6.0 Hz), 1.02 (s, 9H); 75 MHz ^{13}C NMR δ 212.9, 146.8, 141.6, 136.4, 132.5, 128.6, 127.8, 121.0, 116.9, 111.1, 109.3, 55.3, 53.4, 44.4, 44.2, 25.6; HRMS calcd for $C_{20}H_{24}ClNO_2$ 345.1496, found 345.1491.

3-(2-Methoxyphenyl)amino-3-(4-chlorophenyl)-*N*-methyl-*N*-methoxypropanamide (3c). Compound **3c** was isolated as a brown oil (86%): R_f = 0.11 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3394.7, 1654.6 cm^{-1}; 300 MHz ^{1}H NMR δ 7.37 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz), 6.78 (dd, 1H, J = 8.0, 2.0 Hz), 6.67 (td, 1H, J = 8.0, 2.0 Hz), 6.63 (td, 1H, J = 8.0, 2.0 Hz), 6.36 (dd, 1H, J = 8.0, 2.0 Hz), 5.31 (s, 1H), 4.87 (m, 1H), 3.88 (s, 3H), 3.58 (s, 3H), 3.15 (s, 3H), 3.01 (dd, 1H, J = 15.0, 8.0 Hz), 2.92 (dd, 1H, J = 15.0, 6.0 Hz); 75 MHz ^{13}C NMR δ 171.2, 146.9, 141.6, 136.5, 132.7, 128.7, 127.8, 120.9, 116.8, 111.1, 109.3, 61.2, 55.4, 54.1, 40.0, 31.9; HRMS calcd for $C_{18}H_{21}ClN_2O_3$ 338.1241, found 348.1238.

3-(2-Methoxyphenyl)amino-3-(4-chlorophenyl)-*N,N*-dimethylpropanamide (3d). Compound **3d** was isolated as

(23) See the Supporting Information.

a brown oil (96%): R_f = 0.27 (SiO_2, 10% diethyl ether/CH_2Cl_2); IR (thin film) 3384.1, 1644.0 cm^{-1}; 300 MHz ^1H NMR δ 7.36 (d, 2H, J = 9.0 Hz), 7.27 (d, 2H, J = 9.0 Hz), 6.75 (dd, 1H, J = 9.0, 3.0 Hz), 6.69 (td, 1H, J = 9.0, 3.0 Hz), 6.62 (td, 1H, J = 9.0, 3.0 Hz), 6.32 (dd, 1H, J = 9.0, 3.0 Hz), 5.37 (s, 1H), 4.83 (m, 1H), 3.88 (s, 3H), 2.93−2.78 (m, 8H); 75 MHz ^{13}C NMR δ 169.8, 146.9, 141.5, 136.3, 132.5, 128.5, 127.7, 120.7, 116.7, 111.0, 109.2, 55.3, 54.2, 40.6, 37.1, 35.2; HRMS calcd for $C_{18}H_{21}ClN_2O_2$ 332.1292, found 332.1283.

***N*-[3-(2-Methoxyphenyl)amino-3-(4-chlorophenyl)-1-oxopropane]morpholine (3e).** Compound **3e** was isolated as a brown oil which crystallized on standing (94%): mp = 145−146 °C; R_f = 0.30 (SiO_2, 20% diethyl ether/CH_2Cl_2); IR (thin film) 3384.1, 1638.7, 1224.9, 1113.4 cm^{-1}; 300 MHz ^1H NMR δ 7.34 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz), 6.76 (dd, 1H, J = 8.0, 2.0 Hz), 6.69 (td, 1H, J = 8.0, 2.0 Hz), 6.63 (td, 1H, J = 8.0, 2.0 Hz), 6.32 (dd, 1H, J = 8.0, 2.0 Hz), 5.30 (s, 1H), 4.85 (m, 1H), 3.88 (s, 3H), 3.62−3.52 (m, 4H), 3.44−3.41 (m, 2H), 3.29−3.26 (m, 2H), 2.92 (dd, 1H, J = 14.0, 7.0 Hz), 2.80 (dd, 1H, J = 14.0, 6.0 Hz); 75 MHz ^{13}C NMR δ 168.7, 146.9, 141.4, 136.4, 133.0, 128.9, 127.8, 121.0, 117.0, 111.1, 109.3, 66.7, 66.3, 55.5, 54.5, 46.3, 41.9, 40.2. Anal. Calcd for $C_{20}H_{23}ClN_2O_3$: C, 64.08; H, 6.18; N, 7.47. Found: C, 64.22; H, 6.13; N, 7.46.

Methyl 3-(2-Methoxy-5-methylphenyl)amino-3-(4-chlorophenyl)propanoate (3f). Compound **3f** was isolated as a yellow oil (93%): R_f = 0.20 (SiO_2, 40% hexane/CH_2Cl_2); IR (thin film) 3415.9, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 7.32 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz), 6.66 (d, 1H, J = 9.0 Hz), 6.44 (dd, 1H, J = 9.0, 3.0 Hz), 6.25 (d, 1H, J = 3.0 Hz), 4.95 (s, 1H), 4.82 (m, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 2.86 (dd, 1H, J = 15.0, 8.0 Hz), 2.79 (dd, 1H, J = 15.0, 6.0 Hz), 2.13 (s, 3H); 75 MHz ^{13}C NMR δ 171.0, 144.8, 140.8, 135.9, 132.8, 130.2, 128.7, 127.6, 117.2, 112.1, 109.4, 55.5, 53.9, 51.7, 42.6, 20.9; HRMS calcd for $C_{18}H_{20}ClNO_3$ 333.1132, found 333.1135.

Methyl 3-(2-*N*,*N*-Dimethylaminophenyl)amino-3-(4-chlorophenyl)propanoate (3g). Compound **3g** was isolated as a brown oil (97%): R_f = 0.25 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3352.3, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 7.31 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz), 7.03 (dd, 1H, J = 9.0, 3.0 Hz), 6.84 (td, 1H, J = 9.0, 3.0 Hz), 6.46 (td, 1H, J = 9.0, 3.0 Hz),6.35 (dd, 1H, J = 9.0, 3.0 Hz), 5.48 (d, 1H, J = 7.0 Hz), 4.81 (m, 1H), 3.65 (s, 3H), 2.89−2.75 (m, 2H), 2.67 (s, 6H); 75 MHz ^{13}C NMR δ 171.0, 141.1, 141.0, 140.4, 132.8, 128.7, 127.5, 124.4, 119.1, 117.2, 111.1, 54.2, 51.7, 43.9, 43.1; HRMS calcd for $C_{18}H_{21}ClN_2O_2$ 332.1291, found 332.1288.

Methyl 3-(3-Methyl-2-pyridyl)amino-3-(4-chlorophenyl)-propanoate (3h). The reaction was quenched with saturated ammonium chloride, and **3h** was isolated as a brown oil that crystallized on standing to afford tan prisms (95%): mp = 101−102 °C; R_f = 0.33 (SiO_2, 20% diethyl ether/CH_2Cl_2); IR (thin film) 3394.7, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 7.34−7.22 (m, 5H), 6.63 (d, 1H, J = 7.0 Hz), 6.32 (d, 1H, J = 8.0 Hz), 5.21 (d, 1H, J = 7.0 Hz), 5.10 (m, 1H), 3.64 (s, 3H), 2.89 (dd, 1H, J = 15.0, 7.0 Hz), 2.80 (dd, 1H, J = 15.0, 6.0 Hz), 2.34 (s, 3H); 75 MHz ^{13}C NMR δ 171.1, 156.9, 156.8, 140.4, 137.9, 133.1, 128.8, 127.7, 113.0, 103.6, 52.4, 51.9, 41.9, 24.2. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19. Found: C, 63.17; H, 5.69; N, 9.25.

Methyl 3-(2,4-Dimethoxyphenyl)amino-3-(3-pyridyl)-propanoate (3i). The reaction was quenched with saturated ammonium chloride, and **3i** was isolated as a yellow oil which crystallized on standing to afford small tan needles (95%): mp = 93−94 °C; R_f = 0.14 (SiO_2, 20% diethyl ether/CH_2Cl_2); IR (thin film) 3384.1, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 8.63 (s 1H), 8.49 (d, 1H, J = 6.0 Hz), 7.68 (d, 1H, J = 9.0 Hz), 7.23 (dd, 1H, J = 9.0, 6.0 Hz), 6.43 (d, 1H, J = 3.0 Hz), 6.33 (d, 1H, J = 9.0 Hz), 6.25 (dd, 1H, J = 9.0, 3.0 Hz), 4.84 (s, 1H), 4.69 (m, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 2.90 (dd, 1H, J = 15.0, 8.0 Hz), 2.83 (dd, 1H, J = 15.0, 6.0 Hz); 75 MHz ^{13}C NMR δ 171.0, 152.5, 148.2, 138.1, 134.3, 130.0, 123.7, 112.0, 103.5, 99.2, 55.6, 53.3, 51.9, 42.4. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.76; H, 6.21; N, 8.64.

Methyl 3-(2-Methoxyphenyl)amino-5-phenyl-4-pentenoate (3j). Compound **3j** was isolated as a yellow oil (96%): R_f = 0.29 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3410.6, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 7.36−7.20 (m, 5H), 6.87−6.77 (m, 2H), 6.72−6.68 (m, 2H), 6.57 (d, 1H, J = 16.0 Hz), 6.21 (dd, 1H, J = 16.0, 6.0 Hz), 4.67 (s, 1H), 4.51 (m, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 2.81 (dd, 1H, J = 15.0, 7.0 Hz), 2.72 (dd, 1H, J = 15.0, 7.0 Hz), 2.13 (s, 3H); 75 MHz ^{13}C NMR δ 171.4, 146.8, 136.4, 130.6, 129.7, 128.3, 127.4, 126.4, 121.0, 116.8, 110.1, 109.5, 55.2, 552.0, 51.5, 40.2; HRMS calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1521.

Methyl 3-(2-Methoxyphenyl)amino-4-*tert*-butyldimethylsiloxybutanoate (3k). The reaction was quenched with saturated ammonium chloride, and **3k** was isolated as a yellow oil (81%): R_f = 0.37 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3409.9, 1736.3 cm^{-1}; 300 MHz ^1H NMR δ 6.85 (td, 1H, J = 8.0, 2.0 Hz), 6.75 (dd, 1H, J = 8.0, 2.0 Hz), 6.69−6.33 (m, 2H), 4.68 (s, 1H), 3.94 (m, 1H), 3.82 (s, 3H), 3.75 (dd, 1H, J = 10.0, 3.0 Hz), 3.68 (dd, 1H, J = 10.0, 5.0 Hz), 3.67 (s, 3H), 2.64 (d, 2H, J = 6.0 Hz), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); 75 MHz ^{13}C NMR δ 172.6, 147.2, 136.5, 121.2, 116.7, 110.7, 109.7, 63.8, 55.3, 51.5, 51.0, 35.7, 25.7, 18.2, −5.6, −5.5; HRMS calcd for $C_{18}H_{31}NO_4Si$ 353.2022, found 353.2018.

Methyl 3-(2-Methoxyphenyl)amino-3-furanylpropanoate (3l). Compound **3l** was isolated as a yellow oil which crystallized on standing (97%): mp = 40−42 °C; R_f = 0.22 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3394.7, 1734.2 cm^{-1}; 300 MHz ^1H NMR δ 7.33 (d, 1H, J = 2.0 Hz), 6.85−6.76 (m, 2H), 6.72−6.66 (m, 2H), 6.27 (dd, 1H, J = 3.0, 2.0 Hz), 6.20 (d, 1H, J = 3.0 Hz), 5.03 (m, 1H), 4.80 (d, 1H, J = 9.0 Hz)), 3.84 (s, 3H), 3.67 (s, 3H), 3.00−2.83 (m, 2H); 75 MHz ^{13}C NMR δ 171.3, 154.5, 147.1, 141.8, 136.2, 121.1, 117.4, 111.1, 110.2, 109.7, 106.2, 55.4, 51.8, 48.6, 20.3. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 64.55; H, 6.22; N, 5.09. Found: C, 65.67; H, 6.35; N, 5.04.

Methyl 3-(2-Methoxyphenyl)amino-4,4-dimethylpentanoate (3m). Compound **3m** was isolated as a yellow oil (58%): R_f = 0.33 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3415.5, 1738.4 cm^{-1}; 300 MHz ^1H NMR δ 6.86−6.73 (m, 3H), 6.62−6.57 (m, 1H), 4.26 (d, 1H, J = 9.0 Hz), 3.83 (s, 3H), 3.76 (m, 1H), 3.53 (s, 3H), 2.64 (dd, 1H, J = 15.0, 6.0 Hz), 2.36 (dd, 1H, J = 15.0, 9.0 Hz), 0.96 (s, 9H); 75 MHz ^{13}C NMR δ 173.1, 146.3, 138.3, 121.2, 115.8, 110.5, 109.6, 59.1, 55.5, 51.1, 37.0, 35.7, 26.4; HRMS calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1684.

Methyl 3-(2-Methoxyphenyl)amino-5-*tert*-butyldimethylsiloxypentanoate (3n). The reaction was quenched saturated ammonium chloride, and **3n** was isolated as a yellow oil (96%): R_f = 0.11 (SiO_2, 20% hexane/CH_2Cl_2); IR (thin film) 3409.4, 1737.9 cm^{-1}; 300 MHz ^1H NMR δ 6.85 (td, 1H, J = 8.0, 2.0 Hz), 6.75 (dd, 1H, J = 8.0, 1.0 Hz), 6.70−6.61 (m, 2H), 4.55 (s, 1H), 4.01 (m, 1H), 3.82 (s, 3H), 3.75−3.68 (m, 2H), 3.65 (s, 3H), 2.68 (dd, 1H, J = 15.0, 6.0 Hz), 2.54 (dd, 1H, J = 15.0, 7.0 Hz), 1.92−1.75 (m, 2H), 0.90 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); 75 MHz ^{13}C NMR δ 172.3, 146.9, 136.9, 121.2, 116.3, 110.3, 109.5, 60.1, 55.3, 51.5, 47.5, 39.0, 37.3, 25.9, 18.2, 12.5, −5.5; HRMS calcd for $C_{19}H_{33}NO_4Si$ 367.2179, found 367.2169.

Methyl 3-(2-Methoxyphenyl)amino-5-phenylpentanoate (3o). Compound **3o** was isolated as a yellow oil (87%): R_f = 0.11 (SiO_2, 1/40/59% diethyl ether/hexane/CH_2Cl_2); IR (thin film) 3405.3, 1728.9 cm^{-1}; 300 MHz ^1H NMR δ 7.30−7.25 (m, 2H), 7.21−7.16 (m, 3H), 6.86 (td, 1H, J = 8.0, 1.0 Hz), 6.78 (dd, 1H, J = 8.0, 1.0 Hz), 6.66 (td, 1H, J = 8.0, 1.0 Hz), 6.60 (dd, 1H, J = 8.0, 1.0 Hz), 4.30 (s, 1H), 3.89−3.81 (m, 4H), 3.64 (s, 3H), 2.81−2.62 (m, 3H), 2.49 (dd, 1H, J = 15.0, 7.0 Hz), 2.05−1.85 (m, 2H); 75 MHz ^{13}C NMR δ 172.2, 146.9, 141.5, 136.8, 128.3, 128.2, 125.8, 121.2, 116.5, 110.3, 109.6, 55.3, 51.5, 49.4, 39.3, 36.7, 32.3; HRMS calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1679.

Multicomponent Array. The array was run using a standard 96-well plate in a glovebox under an inert atmo-

sphere of N_2. Vials containing solutions of the aldehydes (0.5 M), anilines (0.52 M), and the α-bromo compounds (0.52 M) in 1,2-dichloroethane were transferred into the glovebox. Using a stepping pipet, a 50 μL aliquot of the aldehyde (25 μmol) followed by a 50 μL aliquot of the aniline (26 μmol) were combined in the appropriate wells of the plate. The wells were then covered to minimize evaporation. After 30 min, a 45 μL aliquot of a solution of $Zn(CH_3)_2$ (2 M in toluene) was added to the aldehyde and aniline mixtures with an eight-tip pipet, and again the wells were covered. After 15 min, a 50 μL aliquot of the α-bromo compound solutions (26 μmol) was added to the wells using the stepping pipet. The Ni catalyst was then dissolved in CH_2Cl_2 (0.025 M), and 50 μL of the solution (1.25 μmol) was added to each well using an eight-tip pipet. The wells were then covered. After 1.5 h, 10 μL aliquots were taken from six random wells for TLC analysis, all indicated complete reaction. The 96-well plate was then taken from the glovebox, and using an eight-tip pipet, the reactions were quenched by passing them across neutral alumina that had been covered with a thin layer of activated charcoal. Vacuum was applied to pull the reaction mixtures through the alumina, which was subsequently rinsed with a total of 600 μL of acetonitrile (ACN) per well. Aliquots of the resulting product solutions were diluted further in ACN for LCMS analysis.

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Supporting Information Available: Representative ^1H NMR and ^{13}C NMR spectra; UV and total ion chromatograms and low-resolution mass spectra for all array compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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