Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201300904

Biomimetic Aerobic C–H Olefination of Cyclic Enaminones at Room Temperature: Development toward the Synthesis of 1,3,5-Trisubstituted Benzenes

Yi-Yun Yu[a] and Gunda I. Georg[a,*]

[a] Department of Chemistry, Department of Medicinal Chemistry and the Institute for Therapeutics Discovery and Development, University of Minnesota, Twin Cities, 717 Delaware St SE, Minneapolis, Minnesota 55414, USA
Fax: (+1)-612-626-6318; e-mail: georg@umn.edu

Received: October 9, 2013; Revised: November 17, 2013; Published online: January 31, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300904.

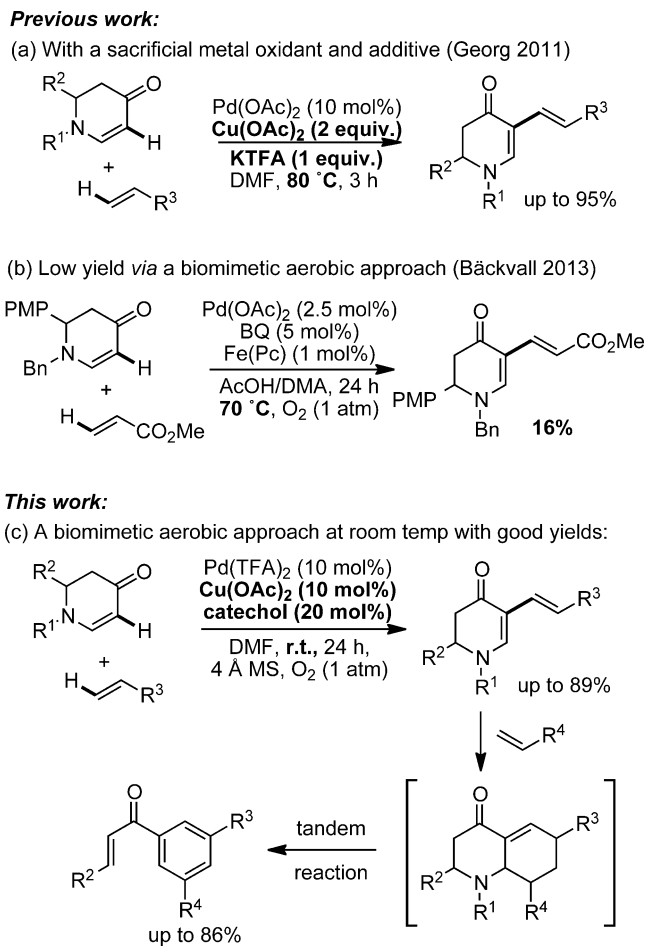
Abstract: A green and mild protocol for the dehydrogenative olefination of cyclic enaminones was devised *via* palladium catalysis at room temperature using oxygen as the terminal oxidant. The synthetic utility of the olefinated cyclic enaminones afforded a series of unique 1,3,5-trisubstituted benzenes *via* an unanticipated Diels–Alder tandem reaction. The broad substrate scope and good yields achieved with this new protocol provide an alternative pathway for arene functionalization.

Keywords: arenes; C–H activation; cycloaddition; olefination; palladium

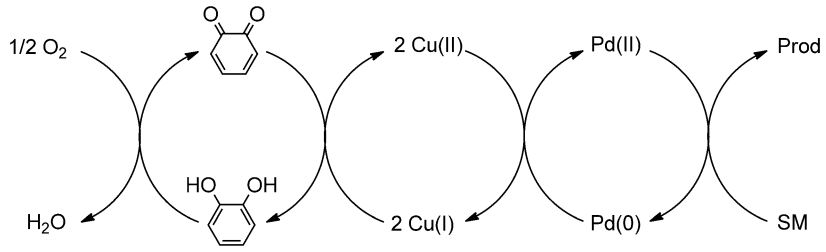
Introduction

1,3-Dienes and polyenes are important structural motifs found in many pharmaceutically active compounds and natural products, such as carotenes, vitamin A, bombykol, etc.[1] Synthesis of these compounds can be categorized into two classes: (i) carbonyl olefination reactions,[2] represented by the Wittig reaction[3] and (ii) cross-olefination coupling, represented by the Heck reaction.[4] In the interests of atom economy, new methods that in addition generate minimal waste are highly desirable.[5]

Dehydrogenative cross-coupling of alkenes, arguably the ideal pathway for diene synthesis, surprisingly did not attract much attention until very recently. Examples of this kind are limited.[6] We recently developed a Pd-catalyzed cross dehydrogenative olefination of cyclic enaminones (Scheme 1a).[7] Despite the high yields and broad scope, our protocol requires *stoichiometric* amounts of a Cu(II) oxidant and an additive, as well as elevated temperature (80 °C). This demand for sacrificial heavy metal oxidants is very common in the current field and is ironically contradictory to the goals of C–H functionalization (e.g., reducing heavy metal waste).[8] In search for alternative green oxidants, molecular oxygen is the ideal candi-



Scheme 1. C–H alkenylation of cyclic enaminones.



Scheme 2. Biomimetic aerobic Pd catalysis with catechol.

date because of its inexpensive and eco-friendly nature.[5]

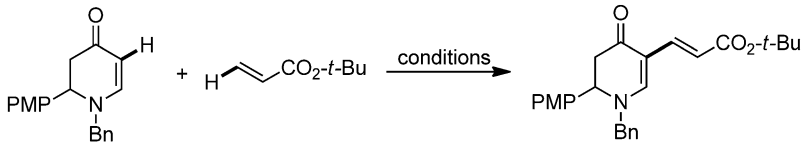
The obstacle of applying O_2 as the sole oxidant is the high activation energy and low concentration of O_2 in solutions, which significantly impedes the direct oxidation of Pd(0). To circumvent the high pressure of O_2 used in early development,[5b,8c] catalytic amounts of O_2 activators, such as molybdovanadophosphoric acid (HPMoV) and benzoquinone, were introduced to promote oxidation in a biomimetic approach.[5a,8c,9] Mechanistically, this biomimetic strategy divides the oxidation process into several interconnected redox cycles and thereby effectively reduces the initial high energy barrier for electron transfer.[9] For example, Hosokawa discovered that inexpensive catechol and Cu(II) could remarkably enhance Pd(II) catalysis in the presence of O_2 (Scheme 2).[10] Catechol is thought to act as *ortho*-quinone that incorporates Cu(II) as a ligand. With regard to dehydrogenative cross-couplings of alkenes, the use of O_2 as a terminal oxidant is very rare and there has been no report of this type of reaction to proceed at room temperature.[11] Bäckvall reported a versatile biomimetic aerobic coupling between two alkenes under low catalyst loading.[11e] However, their method, involving acidic media, failed to deliver a satisfactory outcome for cyclic enaminones (Scheme 1b).

In our continuing efforts in generating libraries for biological screening, we are particularly interested in functionalizing the *non-aromatic* cyclic enaminones as unique piperidine surrogates for alkaloid synthesis.[12] Our aforementioned protocol has furnished various alkenylated enaminones, but their synthetic utility had remained unexplored. In light of the recent advances in aerobic C–H functionalization, we first developed a greener and milder method for dehydrogenative olefination of cyclic enaminones at *room temperature* (Scheme 1c). Next, we envisioned the resulting dienes participating in a Diels–Alder reaction to gain a quick access to hydroquinolines, a key structural motif in several major classes of alkaloids.[13] The serendipitous discovery of a Diels–Alder tandem reaction, however, led to the formation of a series of distinctive 1,3,5-trisubstituted benzenes, which are important structural motifs in material science[14] and medicinal chemistry[15] because of their unique symmetry. Herein, we disclose our recent efforts in improving the C–H olefination of cyclic enaminones and its unexpected application in the synthesis of 1,3,5-trisubstituted arenes.

Results and Discussion

We started by probing aerobic conditions for the dehydrogenative olefination of enaminones under atmospheric pressure (Table 1). To better compare the optimization with our first protocol,[7] the same enaminone **1** and alkene **2** were chosen for the current optimization study. Compared to our reported result (87%, entry 1),[7] the yield dropped significantly to 27% under air without a Cu(II) oxidant (entry 2). Applying pure O_2 instead of air increased the yield to 44% (entry 3). Attempts to use 20 mol% of $Cu(OAc)_2$ showed no improvement of the yield (entry 4). In order to activate O_2, catalytic amounts of catechol were tested (entries 5–7). Initially, the temperature with $Pd(OAc)_2$/$Cu(OAc)_2$/catechol was set at 80 °C, but no beneficial effect was observed (entry 5). After examining various catalyst loadings and temperatures, we were pleased to see a significant increase of yield to 78% in the presence of $Pd(OAc)_2$ (10 mol%) with $Cu(OAc)_2$ and catechol in a 1:1:2 ratio (entry 6). Remarkably, the coupling proceeded smoothly at *room temperature*. A similar increase on yield was also observed under air, albeit less optimal than that under O_2 (entry 7). A series of common solvents was also assessed in addition to DMF (entries 8–10). Although no other solvents improved the olefination outcome, the relatively higher yields from polar solvents (e.g., DMSO, MeCN) indicate that their coordinating ability might help to extend the catalyst lifespan, reflecting on the higher yields. As Hosokawa had reported the importance of interchangeable anionic ligands for the catalyst efficacy,[10a] we next evaluated a few anions (i.e., TFA^-, OAc^-, and Cl^-, entries 11–13). The blend of $Pd(TFA)_2$ and $Cu(OAc)_2$ furnished a higher yield (81%, entry 11) compared to those from the OAc^-/Cl^- or TFA^-/Cl^- systems (entries 12 and 13). Presumably, the combination of TFA^- and OAc^- may sufficiently increase the electrophilicity of the Pd(II) center for palladation, meanwhile balanc-

Table 1. Optimization of aerobic dehydrogenative olefination of enaminones.



Entry[a]	[Pd] (mol%)	[Cu] (mol%)	Atm.	Additive (mol%)	Solvent	Temp. [°C]	Yield [%][b]
1	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (200)	N_2	KTFA (100)	DMF	80	87 (81[c])
2	$Pd(OAc)_2$ (10)	–	air	KTFA (100)	DMF	80	27
3	$Pd(OAc)_2$ (10)	–	O_2	KTFA (100)	DMF	80	44
4	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (20)	O_2	KTFA (100)	DMF	80	41
5	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	O_2	catechol (10)	DMF	80	40
6	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	DMF	r.t.	78
7	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	air	catechol (20)	DMF	r.t.	66
8	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	DMSO	r.t.	62
9	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	MeCN	r.t.	65
10	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	THF	r.t.	39
11	$Pd(TFA)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	DMF	r.t.	81
12	$PdCl_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20)	DMF	r.t.	57
13	$Pd(TFA)_2$ (10)	$CuCl_2$ (10)	O_2	catechol (20)	DMF	r.t.	27
14	$Pd(TFA)_2$ (10)	$Cu(OAc)_2$ (10)	O_2	catechol (20) + 4 Å MS	DMF	r.t.	91 (89[c])

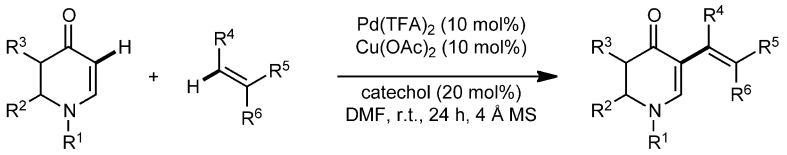
[a] *Other conditions:* **1** (0.10 mmol), **2** (0.40 mmol), balloon (1 atm), solvent (0.5 mL), 24 h (PMP = *para*-methoxyphenyl).
[b] Yields determined by ^1H NMR with Ph_3SiMe (1.0 equiv.) as the internal standard.
[c] Isolated yield. (Detailed optimization is given in the Supporting Information.)

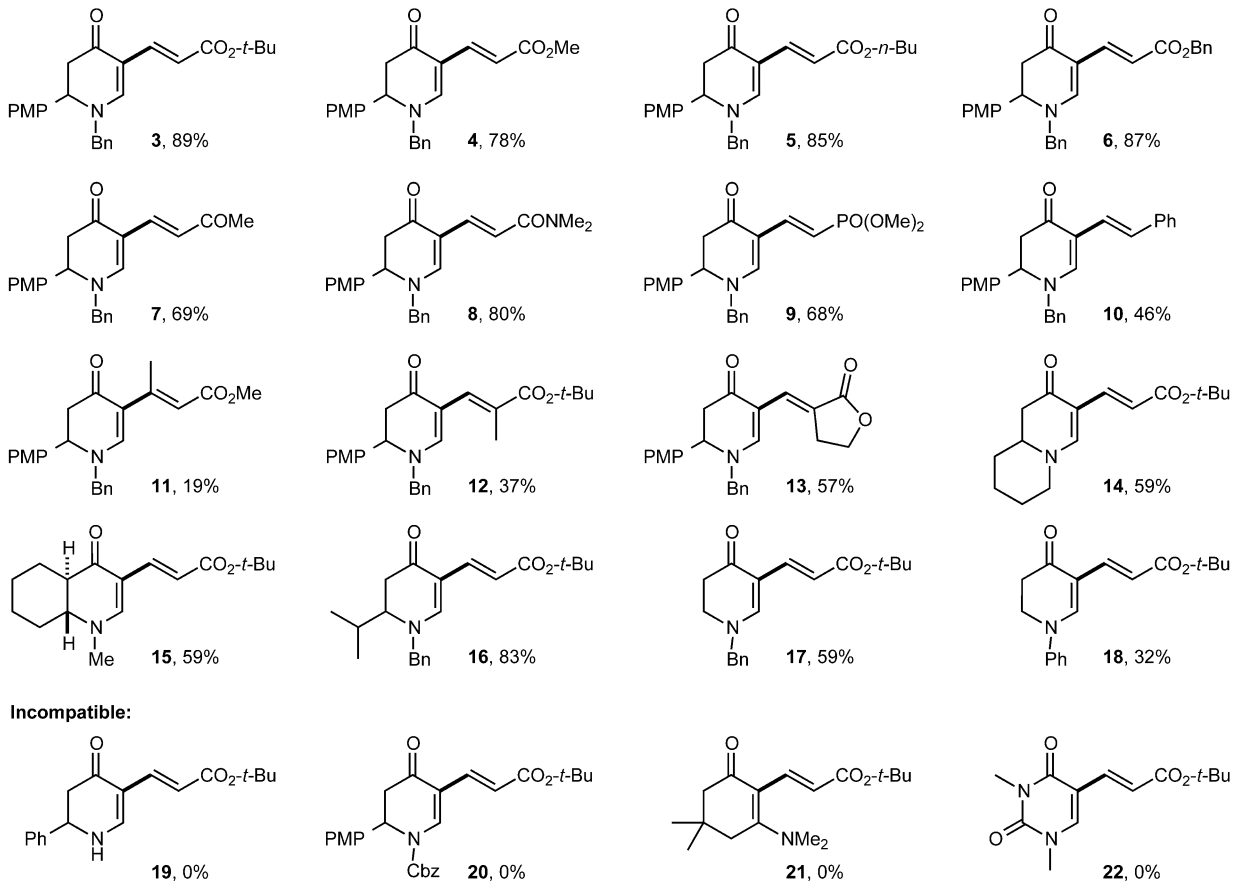
ing the level of acid by-products (i.e., TFA and AcOH) not to decompose the acid-sensitive enaminones. We also investigated the role of bases and reaction concentrations (see Table S6 in the Supporting Information). It soon became clear that bases inhibited the coupling by reducing the yield to 16% and more concentrated solutions (0.2–0.4 M) were favorable in general. Moreover, Stahl reported that molecular sieves were beneficial for Pd-catalyzed aerobic alcohol oxidation, because they could provide a heterogeneous surface that hindered bulk aggregation of Pd(0) metal to increase the catalyst stability.[16] Indeed, the addition of 4 Å MS promoted a full consumption of enaminone **1** and furnished an optimal isolated yield of 89% (entry 14).

Next, we embarked on examining the scope of the reaction (Table 2). Acrylates were excellent alkene sources providing yields of up to 89% (**3**–**6**). The vinyl phosphonate, vinyl ketone, acrylamide, and styrene were all well tolerated (**7**–**10**). In contrast, disubstituted alkenes gave significantly lower yields (**11**–**13**), possibly due to steric hindrance from the substituents that might hinder the migratory insertion. Interestingly, double bond isomerization, common in prior reports,[17] was not observed when more than one β-hydrogen was present in the alkenes. Only conjugated (to enaminone) dienes (**12** and **13**) were isolated. This is contrary to our earlier olefination protocol,[7] where unconjugated (to enaminone) dienes were favored at an elevated temperature (80 °C). We speculate that the conformer after migratory insertion might favor the β-hydride elimination to furnish a *conjugated* diene, whereas at a higher temperature a subsequent re-insertion of the Pd–H species could be promoted to reconstruct the Pd intermediate, which eventually furnishes an *unconjugated* diene as a major product, presumably due to its thermal stability. Moreover, the viability of allyl acetate (representing the class of unactivated alkenes) was examined. Unfortunately, it failed to afford any desired product.

A collection of enaminones was assessed under the optimized conditions as well (Table 2). Bicyclic, electron-rich enaminones offered moderate yields (**14** and **15**). Replacing the 2-aryl group (i.e., PMP) with an alkyl group (i.e., *i*-Pr) retained a good yield (83%, **16**). However, removing the 2-PMP group caused a significant yield decline (to 57%, **17**). The reason behind this observation is yet to be elucidated. As we reported before,[7,18] *N*-phenylenaminone is a less effective substrate, possibly due to its attenuated nucleophilicity. Indeed, it afforded a lower yield (32%, **18**) compared to the *N*-benzyl analogue (57%, **17**). It is worth mentioning that the *N*-H enaminone, *N*-Cbz enaminone, and *E*-enaminone were again all incompatible under the current aerobic conditions (**19**–**21**), albeit consistent with our previous studies.[18,19] Our attempts on the uracil scaffold (**22**) were unfortunately not successful either. Nonetheless, we have devised a greener and milder method to alkenylate cyclic enaminones with comparable yields to our first protocol.

Table 2. Scope of aerobic dehydrogenative olefination of enaminones.[a]



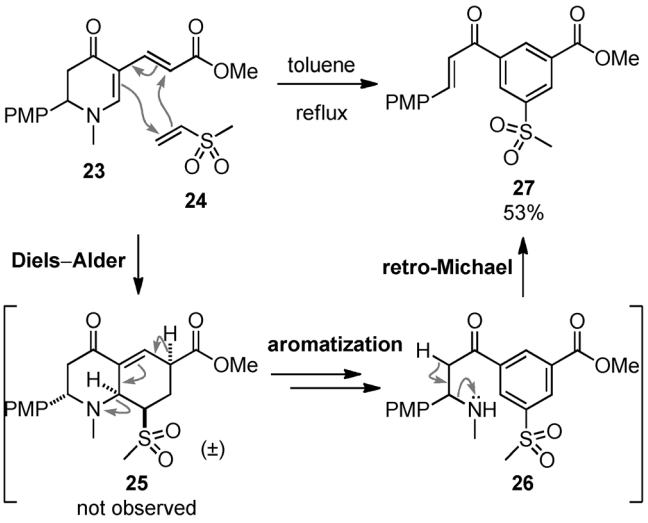


[a] *Conditions:* enaminone (0.10 mmol), alkene (0.40 mmol), $Pd(TFA)_2$ (10 mol%), $Cu(OAc)_2$ (10 mol%), catechol (20 mol%) and 4 Å molecular sieves (*ca.* 30 mg) under O_2 (balloon) in DMF (0.5 mL) at room temperature for 24 h. Isolated yields.

This is also the first example of cross dehydrogenative couplings of alkenes taking place at *room temperature*.

To explore the synthetic utility of our new protocol, we proposed a Diels–Alder reaction to transform the alkenylated enaminones to hydroquinoline analogues, a common structural feature in many alkaloids.[13] In fact, similar amino-substituted dienes have been employed to regio- and stereoselectively construct the octahydroquinoline scaffold in the Comins group.[20] Surprisingly, our attempts on the Diels–Alder reaction between diene **23** and dienophile **24** resulted in the formation of compound **27** instead of the anticipated **25** (Scheme 3). Presumably, the multiple electron-withdrawing substituents and the amino leaving group in cycloadduct **25** promoted aromatization with O_2 present in the reaction.[20a,c,21] Afterwards a retro-Michael fragmentation released methylamine[22] to afford 1,3,5-trisubstituted benzene **27**.

Available methods to synthesize 1,3,5-trisubstituted benzenes mostly depend on commercially available 1,3,5-trihalobenzenes (or the like) as precursors with an established substitution pattern.[14,23] There is a lack of general, regioselective methods to generate *unsymmetrical* 1,3,5-trisubstituted benzenes, which are more valuable in medicinal chemistry than the *symmetrical* ones.[15] Encouraged by our results, we considered the potential of the Diels–Alder tandem reaction to devise an alternative useful method to synthesize 1,3,5-trisubstituted benzenes. We hence tested a series of conditions for the Diels–Alder tandem reaction (Tables S7–S9 in the Supporting Information).



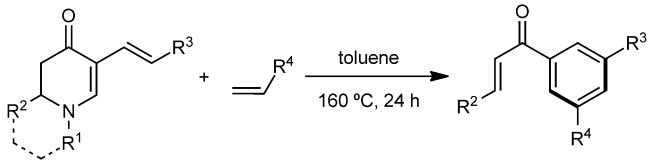
Scheme 3. Formation of 1,3,5-trisubstituted benzenes.

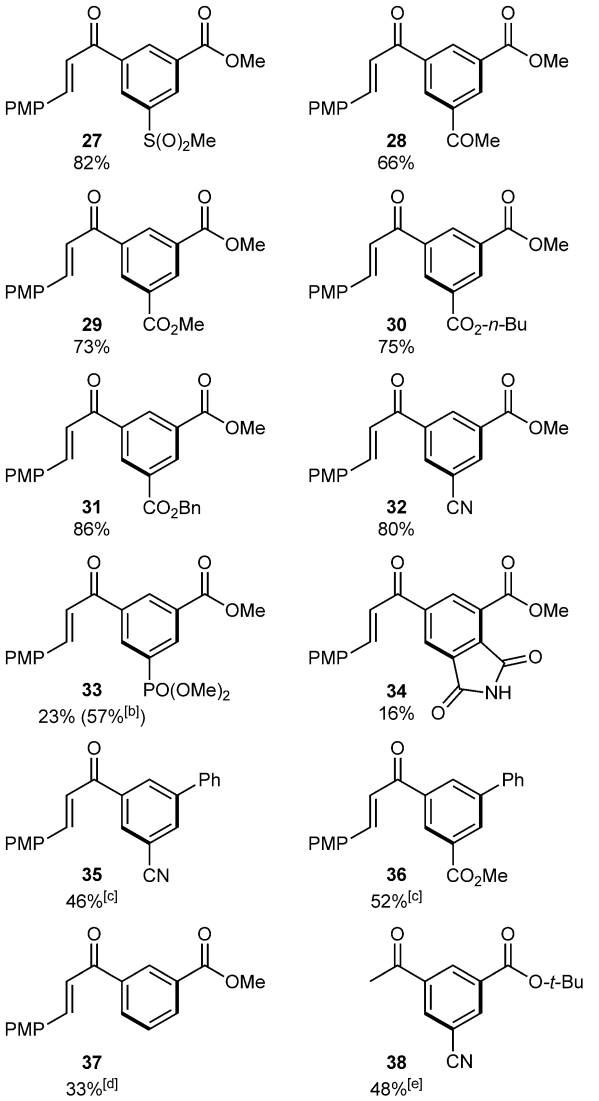
After screening solvents, microwave techniques, temperatures, reaction time, and stoichiometry, we found that 8.0 equiv. of dienophiles in toluene at 160 °C for 24 h delivered the optimal outcome.

The scope of this tandem reaction was then investigated (Table 3). A wide range of electron-deficient dienophiles (e.g., vinyl sulfone, vinyl ketone, acrylates, acrylonitrile, vinyl phosphonate) was viable under the conditions with yields up to 86% (**27**–**33**). However, the maleimide-generating arene **34** was only obtained in a low yield (16%). Although styrene was not reactive as a dienophile, the flexibility of our protocol allowed us to install styrene beforehand (as R^3 in diene **10**) *via* the dehydrogenative olefination, and the tandem reaction thereafter could furnish biphenyls **35** and **36**. When acrylic acid was used, the expected compound **40** was not detected (Scheme 4a). Instead, a decarboxylation occurred to form **37**. Enaminone diene **14** was also subjected to the tandem reaction. Surprisingly, compound **38** was obtained as the final product (Scheme 4b). Due to the unique structural feature in adduct **42**, we postulate that a retro-Mannich reaction took place instead of a retro-Michael fragmentation. It is worth noting that the Diels–Alder reaction exhibited excellent regioselectivity, furnishing a distinctive 1,3,5-trisubstitution pattern. In addition, no octahydroquinoline products (such as **25**) were left after any of these transformations.

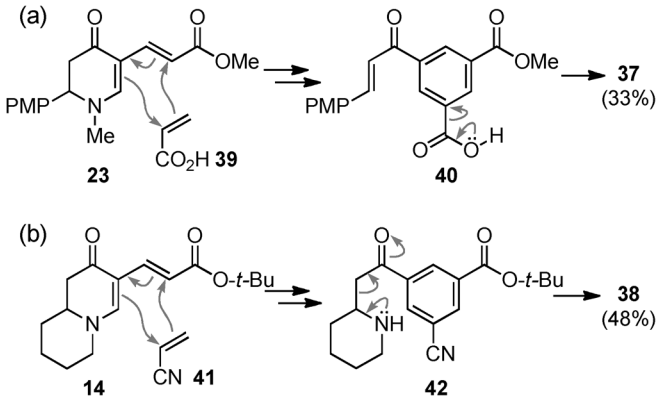
The advantages of the new tandem reaction in regioselectively functionalizing arenes are three-fold. (i) A series of electron-withdrawing groups (EWGs) are compatible. Due to the nature of the dehydrogenative alkenylation and the normal electron demand Diels–Alder reaction, *electron-deficient* alkenes are preferred in both reactions (Table 2 and Table 3). In particular, functionalities such as sulfone (**27**) and phosphonate (**33**) can now be installed onto the phenyl ring from commercially available vinyl reagents in one step, which eliminates the prefunctionalization needed in other methods.[24] (ii) The new protocol provides a direct pathway to synthesize *unsymmetrical*

Table 3. Synthesis of 1,3,5-trisubstituted benzenes *via* the Diels–Alder tandem reaction.[a]





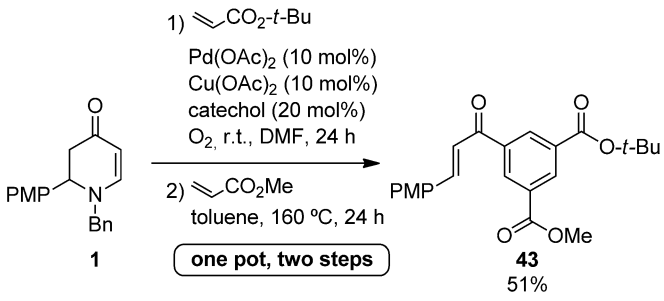
[a] *Conditions:* **23** (0.07 mmol, R^1 = Me, R^2 = PMP, R^3 = CO_2Me), dienophile (0.56 mmol) in toluene (1 mL) at 160 °C, 24 h. Isolated yields.
[b] Based on recovered **23**.
[c] **10** was used as the diene (R^1 = Bn, R^2 = PMP, R^3 = Ph).
[d] Acrylic acid was used as the dienophile.
[e] **14** was used as the diene.



Scheme 4. Tandem reactions featuring (a) decarboxylation and (b) retro-Mannich fragmentation.

1,3,5-EWG-benzenes. The synthesis of this class of arenes is not easy *via* conventional approaches. For instance, the classical electrophilic substitution would suffer severe deactivation by additional EWGs. Metal-catalyzed/mediated cross-couplings would require meticulously 1,3,5-prefunctionalized benzenes with different (pseudo)halogens.[15] As to C–H functionalization, *meta*-selectivity has just started to gain more attention with limited conditions and substrate scope.[25] (iii) The distribution of functional groups can also be easily controlled (e.g., symmetrical **28** *vs.* unsymmetrical **32**). Remarkably, several products, such as **38**, have three orthogonal functionalities that might be modified in a chemoselective manner. In addition, compounds **35** and **36** have also demonstrated the flexibility of changing the sequence of alkenes used in each step to afford satisfactory yields.

Lastly, we also probed the feasibility of a "one-pot, two-step" synthesis of 1,3,5-trisubstituted benzene **43** directly from enaminone **1** (Scheme 5). Cyclic enaminone **1** was sequentially subjected to the aerobic olefination conditions, followed by the Diels–Alder conditions with no purification in between, which eventually furnished 51% of the desired product **43**. Albeit unoptimized, our preliminary results indeed reveal the potential of simply changing alkenes and raising temperatures to generate diverse trisubstituted benzenes in a very convenient manner.



Scheme 5. One-pot synthesis of trisubstituted benzene **43**.

It is worth noting that most of the products (**27**–**37**) are also chalcones, a major class of flavonoids that exhibit a broad spectrum of pharmacological activities (e.g., anti-inflammatory, antiproliferative, antioxidant, and anticancer effects).[26] Previous chalcone syntheses, such as the Claisen–Schmidt condensation[27] or Pd-catalyzed cross-coupling methods,[28] paid most attention to constructing the vinyl ketone linkage of chalcones. Their utilization has been mostly limited by the availability of aryl coupling precursors. In contrast, our approach focuses on the regioselective diversification of arenes, and therefore does not depend as much on the availability of aryl precursors. We expect that the capability to synthesize unique 1,3,5-trisubstituted benzenes shall facilitate the generation of distinctive chalcone libraries for medicinal study.

Conclusions

We have improved the dehydrogenative olefination method for cyclic enaminones *via* a biomimetic approach. The new protocol uses O_2 as the terminal oxidant and significantly reduces the heavy metal oxidant $Cu(OAc)_2$ to a catalytic level. This aerobic C–H olefination reaction shows comparable scope and proceeds smoothly at room temperature, which is reported for the first time for the dehydrogenative cross-couplings of alkenes.

Our synthetic development of olefinated cyclic enaminones unveiled a Diels–Alder tandem reaction, which led to a series of distinctive 1,3,5-trisubstituted benzenes, including chalcones, with good yields. This unexpected transformation shall offer an alternative approach to synthesize both symmetrical and unsymmetrical 1,3,5-trisubstituted benzenes and chalcones for material science and medicinal study, respectively.

Experimental Section

General Information

All reactions were carried out in clear 2-dram vials used without drying. All reagents and anhydrous solvents were purchased and directly used without further purification or drying. Flash column chromatography was carried out on silica gel (230–400 mesh). TLC was conducted on 250 micron, F_{254} silica gel plates. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz with complete proton decoupling. Chemical shifts are reported as ppm relative to chloroform ($CHCl_3$: 7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. IR spectra of solids were obtained by dissolving the sample in CH_2Cl_2 on an NaCl plate. High-resolu-

tion mass spectrometry was performed on an ESI-TOF instrument. Melting points were uncorrected.

Preparation of Starting Materials

For details on the synthesis of starting materials, see the Supporting Information.

General Procedures for the Dehydrogenative Aerobic Olefination of Cyclic Enaminones

In a 2-dram vial, cyclic enaminone (0.10 mmol) was mixed with $Pd(TFA)_2$ (3.3 mg, 0.01 mmol), $Cu(OAc)_2$ (1.8 mg, 0.01 mmol), catechol (2.2 mg, 0.02 mmol) and 4 Å molecular sieves (*ca.* 30 mg). To the mixture was added alkene (0.40 mmol), followed by DMF (0.5 mL). The vial was purged with O_2 and then sealed with an O_2 balloon attached. After being stirred at room temperature for 24 h, the reaction was diluted with acetone (2 mL). The mixture was filtered through Celite, and the filter cake was washed with acetone (20 mL). The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel.

(*E*)-1-Benzyl-5-[2-(*tert*-butoxycarbonyl)vinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (3): Prepared by the general procedure described above and isolated as a light yellow solid; yield: 35.1 mg (89%); mp 64–68 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(methoxycarbonyl)vinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (4): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 28.0 mg (78%); mp 52–55 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(*n*-butoxycarbonyl)vinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (5): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 34.2 mg (85%); mp 102–104 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-5-[2-(Benzoxycarbonyl)vinyl]-1-benzyl-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (6): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 37.4 mg (87%); mp 49–52 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-2-(4-methoxyphenyl)-5-(3-oxobut-1-enyl)-2,3-dihydropyridin-4(1*H*)-one (7): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 23.7 mg (69%); mp 49–52 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(dimethylcarbamoyl)vinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (8): Prepared by the general procedure described above and isolated as a yellow solid; yield: 29.4 mg (80%); mp 51–53 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(diethoxyphosphinyl)vinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (9): Prepared by the general procedure described above and isolated as a yellow wax; yield: 27.4 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (s, 1H), 7.42–7.34 (m, 3H), 7.18–7.07 (m, 4H), 6.95 (dd, $J = 24.7$, 17.1 Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.52 (dd, $J = 22.2$, 17.0 Hz, 1H), 4.51 (t, $J = 6.8$ Hz, 1H), 4.42 (d, $J = 14.9$ Hz, 1H), 4.25 (d, $J = 14.9$ Hz, 1H), 3.81 (s, 3H), 3.72 (d, $J = 3.3$ Hz, 3H), 3.69 (d, $J = 3.2$ Hz, 3H), 2.92 (dd, $J = 16.4$, 7.3 Hz, 1H), 2.70 (dd, $J = 16.3$, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.2$, 160.0, 157.3, 145.4 (d, $J = 8.0$ Hz), 134.7, 129.6, 129.4, 128.9, 128.3, 128.0, 114.8, 106.7 (d, $J = 22.0$ Hz), 104.5 (d, $J = 189.5$ Hz), 60.1, 58.2, 55.5, 52.3 (d, $J = 5.3$ Hz), 52.3 (d, $J = 5.3$ Hz), 44.3; FT-IR (NaCl): $\nu = 3156$, 2953, 2930, 2851, 1654, 1600, 1513, 1457, 1442, 1392, 1358, 1298, 1194, 1179, 1059, 1035, 991, 868, 832 cm^{-1}; HR-MS (ESI+) $m/e = 450.1447$, calculated for $[M+Na]^+$ $C_{23}H_{26}NO_5PNa$: 450.1441.

(*E*)-1-Benzyl-2-(4-methoxyphenyl)-5-styryl-2,3-dihydropyridin-4(1*H*)-one (10): Prepared by the general procedure described above and isolated as a yellow solid; yield: 17.0 mg (46%); mp 54–56 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(methoxycarbonyl)-1-methylvinyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (11): Prepared by the general procedure described above and isolated as a waxy solid; yield: 7.0 mg (19%). Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(*tert*-butoxycarbonyl)propenyl]-2-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (12): Prepared by the general procedure described above and isolated as a waxy solid; yied: 12.2 mg (37%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (s, 1H), 7.50 (d, $J = 0.9$ Hz, 1H), 7.39–7.33 (m, 3H), 7.22–7.12 (m, 4H), 6.88 (d, $J = 8.6$ Hz, 2H), 4.54 (t, $J = 7.0$ Hz, 1H), 4.41 (d, $J = 14.9$ Hz, 1H), 4.26 (d, $J = 14.9$ Hz, 1H), 3.81 (s, 3H), 2.92 (dd, $J = 16.4$, 7.1 Hz, 1H), 2.73 (dd, $J = 16.5$, 6.9 Hz, 1H), 1.90 (d, $J = 1.2$ Hz, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 188.5$, 168.4, 159.9, 154.5, 135.4, 131.9, 130.0, 129.3, 128.7, 128.4, 128.0, 123.0, 114.7, 107.3, 80.0, 60.1, 58.1, 55.5, 43.5, 28.4, 15.2; FT-IR (NaCl): $\nu = 3035$, 2981, 1640, 1594, 1513, 1466, 1442, 1391, 1368, 1299, 1176, 1121, 1035, 833 cm^{-1}; HR-MS (ESI+): $m/e = 456.2144$, calculated for $[M+Na]^+$ $C_{27}H_{31}NO_4Na$: 456.2145.

(*E*)-1-Benzyl-2-(4-methoxyphenyl)-5-[(2-oxodihydrofuran-3(2*H*)-ylidene)methyl]-2,3-dihydropyridin-4(1*H*)-one (13): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 21.2 mg (57%); mp 59–62 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-3-[2-(tert-Butoxycarbonyl)vinyl]-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (14): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 15.5 mg (59%); mp 122–124 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-(*trans*)-3-[2-(*tert*-Butoxycarbonyl)vinyl]-1-methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (15): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 16.4 mg (59%); mp 146–148 °C. Analytical data are consistent with those from our previous report.[7]

(*E*)-1-Benzyl-5-[2-(*tert*-butoxycarbonyl)vinyl]-2-isopropyl-2,3-dihydropyridin-4(1*H*)-one (16): Prepared by the general procedure described above and isolated as a yellow wax; yield: 27.0 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$–7.35 (m, 4H), 7.25 (d, $J = 7.0$ Hz, 2H), 7.08 (d, $J = 15.6$ Hz, 1H), 6.50 (d, $J = 15.6$ Hz, 1H), 4.58 (d, $J = 15.0$ Hz, 1H), 4.48 (d, $J = 15.1$ Hz, 1H), 3.32–3.22 (m, 1H), 2.63 (dd, $J = 16.6$, 7.6 Hz, 1H), 2.47 (dd, $J = 16.6$, 2.3 Hz, 1H), 2.22 (dq, $J = 13.4$, 6.7 Hz, 1H), 1.46 (s, 9H), 0.98 (d, $J = 6.8$ Hz, 3H),

0.92 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 188.7, 168.6, 155.9, 138.9, 135.6, 129.4, 128.9, 127.6, 113.1, 105.9, 79.2, 61.8, 59.8, 37.5, 29.7, 28.4, 19.8, 18.1; FT-IR (NaCl): $\nu=3052$, 2975, 2932, 1685, 1654, 1594, 1496, 1455, 1439, 1391, 1367, 1319, 1271, 1241, 1151, 1093, 990, 859 cm^{-1}; HR-MS (ESI+): $m/e=378.2038$, calculated for $[M+Na]^+$ $C_{22}H_{29}NO_3Na$: 378.2040.

(*E*)-1-Benzyl-5-[2-(*tert*-butoxycarbonyl)vinyl]-2,3-dihydropyridin-4(1*H*)-one (17): Prepared by the general procedure described above and isolated as a yellowish oil; yield: 17.7 mg (59%). Analytical data are consistent with those from our previous report.[7]

(*E*)-5-[2-(*tert*-Butoxycarbonyl)vinyl]-1-phenyl-2,3-dihydropyridin-4(1*H*)-one (18): Prepared by the general procedure described above and isolated as a yellowish solid; yield: 9.0 mg (32%); mp 150–152 °C. Analytical data are consistent with those from our previous report.[7]

General Procedures for the Synthesis of 1,3,5-Trisubstituted Benzenes *via* the Tandem Reaction

In a 2-dram vial, alkenylated cyclic enaminone (0.07 mmol) was mixed with alkene (0.56 mmol) and toluene (1 mL). The vial was then sealed and stirred at 160 °C. After 24 h, the reaction mixture was cooled, concentrated under reduced pressure, and then purified by flash chromatography on silica gel.

(*E*)-Methyl 3-[3-(4-methoxyphenyl)acryloyl]-5-(methylsulfonyl)benzoate (27): Prepared by the general procedure described above and isolated as a yellow solid; yield: 15.0 mg (82%); mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.89 (s, 1H), 8.77 (s, 1H), 8.72 (s, 1H), 7.89 (d, $J=15.4$ Hz, 1H), 7.65 (d, $J=7.8$ Hz, 2H), 7.42 (d, $J=15.5$ Hz, 1H), 6.96 (d, $J=7.8$ Hz, 2H), 4.02 (s, 3H), 3.88 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=187.6$, 164.9, 162.5, 147.3, 142.2, 140.4, 134.0, 132.5, 131.8, 131.1, 131.0, 127.1, 118.1, 114.7, 55.6, 53.1, 44.5; FT-IR (NaCl): $\nu=3055$, 2987, 1732, 1665, 1592, 1571, 1513, 1422, 1325, 1308, 1212, 1174, 1149, 1060, 1030, 984, 961, 896, 828 cm^{-1}; HR-MS (ESI+): $m/e=$ 397.0716, calculated for $[M+Na]^+$ $C_{19}H_{18}O_6SNa$: 397.0716.

(*E*)-Methyl 3-acetyl-5-[3-(4-methoxyphenyl)acryloyl]benzoate (28): Prepared by the general procedure described above and isolated as a yellow solid; yield: 17.5 mg (66%); mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.83$ (s, 1H), 8.78 (s, 1H), 8.75 (s, 1H), 7.86 (d, $J=15.5$ Hz, 1H), 7.65 (d, $J=7.7$ Hz, 2H), 7.46 (d, $J=15.4$ Hz, 1H), 6.96 (d, $J=7.8$ Hz, 2H), 4.00 (s, 3H), 3.87 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=196.8$, 188.7, 165.9, 162.3, 146.4, 139.5, 137.9, 133.4, 132.9, 132.0, 131.5, 130.8, 127.3, 118.7, 114.7, 55.6, 52.8, 27.1; FT-IR (NaCl); $\nu=3055$, 2987, 1728, 1693, 1664, 1599, 1572, 1513, 1422, 1361, 1195, 1173, 1031, 985, 829 cm^{-1}; HR-MS (ESI+): $m/e=361.1044$, calculated for $[M+Na]^+$ $C_{20}H_{18}O_5Na$: 361.1046.

(*E*)-Dimethyl 5-[3-(4-methoxyphenyl)acryloyl] isophthalate (29): Prepared by the general procedure described above and isolated as a yellow solid; yield: 20.3 mg (73%); mp 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$); $\delta=8.88$ (s, 1H), 8.84 (s, 2H), 7.88 (d, $J=15.4$ Hz, 1H), 7.66 (d, $J=$ 7.6 Hz, 2H), 7.46 (d, $J=15.3$ Hz, 1H), 6.97 (d, $J=8.7$ Hz, 2H), 4.01 (s, 6H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=188.6$, 165.8, 162.3, 146.3, 139.4, 134.2, 133.4, 131.4, 130.8, 127.4, 118.8, 114.7, 55.6, 52.8; FT-IR (NaCl): $\nu=3055$, 2987, 2956, 1730, 1664, 1601, 1572, 1513, 1422, 1208, 1173, 1032, 1002, 896, 830 cm^{-1}; HR-MS (ESI+): $m/e=$ 377.1005, calculated for $[M+Na]^+$ $C_{20}H_{18}O_6Na$: 377.0996.

(*E*)-1-Butyl 3-methyl-5-[3-(4-methoxyphenyl)acryloyl] isophthalate (30): Prepared by the general procedure described above and isolated as a yellow wax; yield: 23.2 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.85$ (s, 1H), 8.82 (s, 2H), 7.86 (d, $J=15.3$ Hz, 1H), 7.64 (d, $J=8.1$ Hz, 2H), 7.45 (d, $J=15.3$ Hz, 1H), 6.96 (d, $J=8.2$ Hz, 2H), 4.40 (t, $J=7.2$ Hz, 2H), 4.00 (s, 3H), 3.87 (s, 3H), 1.81 (m, 2H), 1.50 (h, $J=7.4$, 6.9 Hz, 2H), 1.00 (t, $J=8.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=188.7$, 165.8, 165.4, 162.2, 146.3, 139.3, 134.1, 133.4, 133.3, 131.8, 131.3, 130.7, 127.4, 118.8, 114.7, 65.8, 55.6, 52.8, 30.9, 19.4, 13.9; FT-IR (NaCl): $\nu=3053$, 2962, 2936, 1725, 1664, 1601, 1572, 1513, 1464, 1443, 1424, 1386, 1288, 1204, 1173, 1109, 1065, 1032, 986, 828 cm^{-1}; HR-MS (ESI+): $m/e=815.3044$, calculated for $[2M+Na]^+$ $C_{46}H_{48}O_{12}Na$: 815.3038.

(*E*)-1-Benzyl 3-methyl-5-[3-(4-methoxyphenyl)acryloyl] isophthalate (31): Prepared by the general procedure described above and isolated as a yellow wax; yield: 24.0 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.88$ (s, 1H), 8.85 (s, 1H), 8.82 (s, 1H), 7.85 (d, $J=15.5$ Hz, 1H), 7.64 (d, $J=$ 7.8 Hz, 2H), 7.50–7.37 (m, 6H), 6.96 (d, $J=7.8$ Hz, 2H), 5.44 (s, 2H), 3.99 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=188.6$, 165.8, 165.2, 162.2, 146.3, 139.4, 135.7, 134.2, 133.6, 133.5, 131.5, 131.4, 130.8, 128.8, 128.7, 128.6, 127.4, 118.8, 114.7, 67.6, 55.6, 52.8; FT-IR (NaCl): $\nu=3055$, 2987, 1728, 1664, 1601, 1588, 1572, 1513, 1422, 1201, 1173, 1030, 986, 896, 829 cm^{-1}; HR-MS (ESI+): $m/e=453.1314$, calculated for $[M+Na]^+$ $C_{26}H_{22}O_6Na$: 453.1309.

(*E*)-Methyl 3-cyano-5-[3-(4-methoxyphenyl)acryloyl]benzoate (32): Prepared by the general procedure described above and isolated as a light yellow solid; yield: 16.6 mg (80%); mp 257–259 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 8.82 (s, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 7.87 (d, $J=15.4$ Hz, 1H), 7.65 (d, $J=7.2$ Hz, 2H), 7.38 (d, $J=15.4$ Hz, 1H), 6.97 (d, $J=6.8$ Hz, 2H), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=187.3$, 164.7, 162.5, 147.3, 140.0, 136.3, 135.8, 133.0, 132.1, 130.9, 127.1, 117.9, 117.4, 114.8, 113.8, 55.6, 53.2; FT-IR (NaCl): $\nu=3156$, 2957, 2932, 2254, 1794, 1731, 1662, 1600, 1571, 1513, 1465, 1444, 1382, 1307, 1287, 1225, 1173, 1096, 1034, 987, 827 cm^{-1}; HR-MS (ESI+): $m/e=344.0891$, calculated for $[M+Na]^+$ $C_{19}H_{15}NO_4Na$: 344.0893.

(*E*)-Methyl 3-(dimethoxyphosphoryl)-5-[3-(4-methoxyphenyl)acryloyl]benzoate (33): Prepared by the general procedure described above and isolated as a yellow wax; yield: 6.0 mg (23%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.83$ (s, 1H), 8.64 (d, $J=12.1$ Hz, 1H), 8.60 (d, $J=12.1$ Hz, 1H), 7.87 (d, $J=15.6$ Hz, 1H), 7.65 (d, $J=8.6$ Hz, 2H), 7.44 (d, $J=$ 15.5 Hz, 1H), 6.96 (d, $J=8.6$ Hz, 2H), 3.99 (s, 3H), 3.88 (s, 3H), 3.83 (d, $J=11.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=188.5$, 165.7, 162.3, 146.6, 139.4 (d, $J=13.9$ Hz), 136.4 (d, $J=10.9$ Hz), 135.7 (d, $J=11.0$ Hz), 133.2 (d, $J=3.0$ Hz), 131.4 (d, $J=15.2$ Hz), 130.9, 129.1 (d, $J=191.5$ Hz), 127.3, 118.6, 114.7, 55.6, 53.2 (d, $J=5.8$ Hz), 52.9; FT-IR (NaCl): $\nu=3055$, 2987, 1738, 1638, 1512, 1422, 1174, 1033, 896 cm^{-1}; HR-MS (ESI+): $m/e=427.0929$, calculated for $[M+Na]^+$ $C_{20}H_{21}O_7PNa$: 427.0917.

(*E*)-4-Methoxycarbonyl-6-[3-(4-methoxyphenyl)acryloyl]-isoindoline-1,3-dione (34): Prepared by the general proce-

dure described above and isolated as a bright yellow solid; yield: 4.4 mg (16%); mp 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 8.56 (s, 1H), 7.89 (d, J = 15.5 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 15.5 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 4.05 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 165.9, 165.0, 164.5, 162.7, 147.7, 144.0, 134.7, 134.4, 132.7, 131.0, 130.8, 127.0, 125.4, 118.1, 114.8, 55.7, 53.4; FT-IR (NaCl): ν = 3413, 3055, 2987, 1783, 1744, 1638, 1513, 1421, 1173, 896 cm^{-1}; HR-MS (ESI$^+$): m/e = 388.0791, calculated for $[M+Na]^+$ $C_{20}H_{15}NO_6Na$: 388.0792.

(*E*)-3-Cyano-5-[3-(4-methoxyphenyl)acryloyl]-1,1′-biphenyl (35): Prepared by the general procedure described above and isolated as a yellow solid; yield: 10.5 mg (46%); mp 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.88 (d, J = 15.5 Hz, 1H), 7.70–7.62 (m, 4H), 7.51 (m, 3H), 7.40 (d, J = 15.7 Hz, 1H), 6.98 (d, J = 7.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 162.4, 146.7, 143.3, 140.1, 138.3, 134.0, 131.2, 130.8, 130.5, 129.4, 129.0, 127.3, 127.2, 118.6, 118.3, 114.7, 113.6, 55.6; FT-IR (NaCl): ν = 3155, 2929, 2254, 1794, 1710, 1663, 1597, 1571, 1513, 1465, 1382, 1342, 1308, 1288, 1206, 1173, 1095, 1049, 1032, 985, 827 cm^{-1}; HR-MS (ESI$^+$): m/e = 362.1153, calculated for $[M+Na]^+$ $C_{23}H_{17}NO_2Na$: 362.1151.

(*E*)-3-Methoxycarbonyl-5-[3-(4-methoxyphenyl)acryloyl]-1,1′-biphenyl (36): Prepared by the general procedure described above and isolated as a yellow solid; yield: 13.0 mg (52%); mp 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 7.86 (d, J = 15.5 Hz, 1H), 7.73–7.62 (m, 4H), 7.52–7.40 (m, 4H), 6.96 (d, J = 8.0 Hz, 2H), 4.00 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 166.6, 162.1, 145.8, 142.3, 139.5, 139.4, 132.1, 131.3, 131.3, 130.6, 129.2, 128.4, 128.2, 127.6, 127.4, 119.4, 114.6, 55.6, 52.6; FT-IR (NaCl): ν = 3055, 2987, 1723, 1662, 1599, 1572, 1513, 1438, 1422, 1349, 1197, 1173, 1048, 1031, 983, 896, 828 cm^{-1}; HR-MS (ESI$^+$): m/e = 395.1254, calculated for $[M+Na]^+$ $C_{24}H_{20}O_4Na$: 395.1254.

(*E*)-Methyl 3-[3-(4-methoxyphenyl)acryloyl]benzoate (37): Prepared by the general procedure described above and isolated as an off-white solid; yield: 7.6 mg (33%); mp 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.29–8.14 (m, 2H), 7.83 (d, J = 15.5 Hz, 1H), 7.61 (dd, J = 20.1, 8.0 Hz, 3H), 7.44 (d, J = 15.5 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 3.97 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 166.4, 161.9, 145.5, 138.8, 133.4, 132.7, 130.6, 130.4, 129.4, 128.9, 127.4, 119.2, 114.5, 55.4, 52.4; FT-IR (NaCl); ν = 3155, 2984, 2955, 2929, 1793, 1722, 1660, 1595, 1572, 1512, 1466, 1382, 1305, 1291, 1208, 1173, 1096, 1034, 830 cm^{-1}; HR-MS (ESI$^+$): m/e = 319.0946, calculated for $[M+Na]^+$ $C_{18}H_{16}O_4Na$: 319.0941.

***tert*-Butyl 3-acetyl-5-cyanobenzoate (38):** Prepared by the general procedure described above and isolated as a colorless oil; yield: 8.1 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 2.67 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 163.0, 138.2, 136.8, 135.1, 134.1, 133.0, 117.4, 113.7, 83.4, 28.2, 26.8; FT-IR (NaCl): ν = 3055, 2986, 2931, 2238, 1721, 1698, 1639, 1552, 1422, 1371, 1330, 1158, 1129, 978, 896, 844 cm^{-1}; HR-MS (ESI$^+$): m/e = 268.0943, calculated for $[M+Na]^+$ $C_{14}H_{15}NO_3Na$: 268.0944.

"One-Pot, Two-Step" Procedure for the Synthesis of Benzene 43

In a 2-dram vial, cyclic enaminone **1** (0.10 mmol) was mixed with $Pd(TFA)_2$ (3.3 mg, 0.01 mmol), $Cu(OAc)_2$ (1.8 mg, 0.01 mmol), catechol (2.2 mg, 0.02 mmol) and 4 Å molecular sieves (*ca.* 30 mg). To the mixture was added *tert*-butyl acrylate (0.40 mmol), followed by DMF (0.5 mL). The vial was purged with O_2 and then sealed with an O_2 balloon attached. After being stirred at room temperature for 24 h, the reaction mixture was filtered through Celite, and the filter cake was washed with acetone (20 mL). The filtrate was then concentrated and mixed with methyl acrylate (0.80 mmol) and toluene (1 mL). The vial was then sealed and stirred at 160 °C. After 24 h, the reaction mixture was cooled, concentrated, and then purified by flash chromatography on silica gel to afford product **43** as a yellow wax; yield: 20.1 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81–8.76 (m, 3H), 7.85 (d, J = 15.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 15.5 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 166.0, 164.5, 162.2, 146.2, 139.2, 134.0, 133.4, 133.3, 133.0, 131.2, 130.7, 127.4, 118.9, 114.7, 82.5, 55.6, 52.8, 28.3; HR-MS (ESI$^+$): m/e = 397.1650, calculated for $[M+H]^+$ $C_{23}H_{25}O_6$: 397.1646.

Acknowledgements

We greatly appreciate the financial support from the National Institutes of Health (GM081267) and the University of Minnesota through the Vince and McKnight Endowed Chairs (to G.I.G.). We also thank Prof. Jin-Quan Yu and Prof. Dale L. Boger for kindly providing equipment for GC-MS and LC-MS analyses respectively.

References

[1] G. Wang, S. Mohan, E.-i. Negishi, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 11344–11349.
[2] M. Majewski, D. M. Gleave, *Tetrahedron Lett.* **1989**, *30*, 5681–5684.
[3] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
[4] W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2–7.
[5] a) Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381–3430; b) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329–2363.
[6] X. Shang, Z.-Q. Liu, *Chem. Soc. Rev.* **2013**, *42*, 3253–3260.
[7] Y.-Y. Yu, M. J. Niphakis, G. I. Georg, *Org. Lett.* **2011**, *13*, 5932–5935.
[8] a) C. Yeung, V. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; c) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170–1214; d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083.
[9] J. Piera, J.-E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558–3576; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506–3523.

[10] a) Y. Kawamura, Y. Kawano, T. Matsuda, Y. Ishitobi, T. Hosokawa, *J. Org. Chem.* **2009**, *74*, 3048–3053; b) K. Minami, Y. Kawamura, K. Koga, T. Hosokawa, *Org. Lett.* **2005**, *7*, 5689–5692.
[11] a) Y. Hatamoto, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2004**, *6*, 4623–4625; b) Y.-H. Xu, Y. K. Chok, T.-P. Loh, *Chem. Sci.* **2011**, *2*, 1822–1825; c) Y. Bai, J. Zeng, S. Cai, X.-W. Liu, *Org. Lett.* **2011**, *13*, 4394–4397; d) Y.-H. Xu, J. Lu, T.-P. Loh, *J. Am. Chem. Soc.* **2009**, *131*, 1372–1373; e) N. Gigant, J.-E. Bäckvall, *Chem. Eur. J.* **2013**, *19*, 10799–10803.
[12] a) S. V. Tsukanov, D. L. Comins, *Angew. Chem.* **2011**, *123*, 8785–8787; *Angew. Chem. Int. Ed.* **2011**, *50*, 8626–8628; b) F. A. Davis, H. Xu, J. Y. Zhang, *J. Org. Chem.* **2007**, *72*, 2046–2052; c) J. P. Michael, C. B. de Koning, C. W. van der Westhuyzen, *Org. Biomol. Chem.* **2005**, *3*, 836–847; d) T. G. Back, M. D. Hamilton, V. J. J. Lim, M. Parvez, *J. Org. Chem.* **2005**, *70*, 967–972; e) M. J. Niphakis, B. C. Gay, K. H. Hong, N. P. Bleeker, G. I. Georg, *Bioorg. Med. Chem.* **2012**, *20*, 5893–5900; f) M. W. Leighty, G. I. Georg, *ACS Med. Chem. Lett.* **2011**, *2*, 313–315; g) M. J. Niphakis, G. I. Georg, *J. Org. Chem.* **2010**, *75*, 6019–6022; h) D. L. Comins, J. J. Sahn, *Org. Lett.* **2005**, *7*, 5227–5228.
[13] a) M. Saha, R. G. Carter, *Org. Lett.* **2013**, *15*, 736–739; b) Y. Sasaki, D. Kato, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 13533–13544; c) M. Santarem, C. Vanucci-Bacque, G. Lhommet, *J. Org. Chem.* **2008**, *73*, 6466–6469; d) Z. Q. Yuan, H. Ishikawa, D. L. Boger, *Org. Lett.* **2005**, *7*, 741–744; e) S. A. Kozmin, T. Iwama, Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641; f) B. Danieli, G. Lesma, M. Luzzani, D. Passarella, A. Silvani, *Tetrahedron* **1996**, *52*, 11291–11296.
[14] a) P. J. Stackhouse, A. Wilson, D. Lacey, M. Hird, *Liq. Cryst.* **2010**, *37*, 1191–1203; b) C. F. C. Fitié, W. S. C. Roelofs, M. Kemerink, R. P. Sijbesma, *J. Am. Chem. Soc.* **2010**, *132*, 6892–6893; c) T. M. Miller, T. X. Neenan, *Chem. Mater.* **1990**, *2*, 346–349; d) J. Pang, Y. Tao, S. Freiberg, X.-P. Yang, M. D'Iorio, S. Wang, *J. Mater. Chem.* **2002**, *12*, 206–212; e) Y. Yamaguchi, T. Ochi, S. Miyamura, T. Tanaka, S. Kobayashi, T. Wakamiya, Y. Matsubara, Z.-I. Yoshida, *J. Am. Chem. Soc.* **2006**, *128*, 4504–4505.
[15] a) R. C. A. Isaacs, C. L. Newton, K. J. Cutrona, S. P. Mercer, L. S. Payne, K. J. Stauffer, P. D. Williams, J. J. Cook, J. A. Krueger, S. D. Lewis, B. J. Lucas, E. A. Lyle, J. J. Lynch, D. R. McMasters, A. M. Naylor-Olsen, M. T. Michener, A. A. Wallace, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1536–1540; b) J. Georgsson, C. Sköld, B. Plouffe, G. Lindeberg, M. Botros, M. Larhed, F. Nyberg, N. Gallo-Payet, A. Gogoll, A. Karlén, A. Hallberg, *J. Med. Chem.* **2005**, *48*, 6620–6631; c) S. Lindman, G. Lindeberg, F. Nyberg, A. Karlén, A. Hallberg, *Bioorg. Med. Chem.* **2000**, *8*, 2375–2383; d) B. Liu, R. S. Shetty, K. K. Moffett, M. J. Kelly, *Tetrahedron Lett.* **2011**, *52*, 1680–1684.
[16] B. A. Steinhoff, A. E. King, S. S. Stahl, *J. Org. Chem.* **2006**, *71*, 1861–1868.
[17] a) Y.-Y. Yu, G. I. Georg, *Chem. Commun.* **2013**, *49*, 3694–3696; b) M. Miyasaka, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2010**, *75*, 5421–5424; c) M. Min, Y. Kim, S. Hong, *Chem. Commun.* **2013**, *49*, 196–198; d) N. Gigant, I. Gillaizeau, *Org. Lett.* **2012**, *14*, 3304–3307.
[18] a) Y. W. Kim, M. J. Niphakis, G. I. Georg, *J. Org. Chem.* **2012**, *77*, 9496–9503; b) Y.-Y. Yu, L. Bi, G. I. Georg, *J. Org. Chem.* **2013**, *78*, 6163–6169.
[19] a) L. Bi, G. I. Georg, *Org. Lett.* **2011**, *13*, 5413–5415; b) H. Ge, M. J. Niphakis, G. I. Georg, *J. Am. Chem. Soc.* **2008**, *130*, 3708–3709.
[20] a) D. L. Comins, J. T. Kuethe, T. M. Miller, F. C. Fevrier, C. A. Brooks, *J. Org. Chem.* **2005**, *70*, 5221–5234; b) J. T. Kuethe, C. A. Brooks, D. L. Comins, *Org. Lett.* **2003**, *5*, 321–323; c) J. T. Kuethe, D. L. Comins, *Tetrahedron Lett.* **2003**, *44*, 4179–4182.
[21] G. J. Bodwell, K. M. Hawco, R. P. da Silva, *Synlett* **2003**, 179–182.
[22] In the presence of an excess amount of dienophile (e.g., methyl acrylate), methylamine could readily undergo an aza-Michael addition, the product of which was detected by LC-MS. See the Supporting Information for more details.
[23] a) E. Karpuk, D. Schollmeyer, H. Meier, *Eur. J. Org. Chem.* **2007**, 1983–1990; b) M. W. Majchrzak, J. N. Zobel, D. J. Obradovich, G. A. Peterson, *Org. Prep. Proced. Int.* **1997**, *29*, 361–364.
[24] a) G. Yuan, J. Zheng, X. Gao, X. Li, L. Huang, H. Chen, H. Jiang, *Chem. Commun.* **2012**, *48*, 7513–7515; b) D. A. Alonso, M. Fuensanta, C. Nájera, M. Varea, *J. Org. Chem.* **2005**, *70*, 6404–6416; c) C. Bardelle, T. Coleman, D. Cross, S. Davenport, J. G. Kettle, E. J. Ko, A. G. Leach, A. Mortlock, J. Read, N. J. Roberts, P. Robins, E. J. Williams, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5717–5721; d) K. Pilgram, F. Korte, *Tetrahedron* **1964**, *20*, 177–187; e) C. A. Dvorak, C. Liu, J. Shelton, C. Kuei, S. W. Sutton, T. W. Lovenberg, N. I. Carruthers, *ACS Med. Chem. Lett.* **2012**, *3*, 637–639; f) T.-B. Liao, Y. Ling, Z.-X. Chen, Y.-M. Zhou, L.-H. Weng, *Chem. Commun.* **2010**, *46*, 1100–1102; g) P. Garczarek, J. Janczak, J. Zoń, *J. Mol. Struct.* **2013**, *1036*, 505–509.
[25] a) H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567–7571; b) D. W. Robbins, J. F. Hartwig, *Angew. Chem.* **2013**, *125*, 967–971; *Angew. Chem. Int. Ed.* **2013**, *52*, 933–937; c) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884; d) T. Truong, O. Daugulis, *Angew. Chem.* **2012**, *124*, 11845–11847; *Angew. Chem. Int. Ed.* **2012**, *51*, 11677–11679; e) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518–522; f) E. Y. Lee, J. Park, *ChemCatChem* **2011**, *3*, 1127–1129; g) J. Cornella, M. Righi, I. Larrosa, *Angew. Chem.* **2011**, *123*, 9601–9604; *Angew. Chem. Int. Ed.* **2011**, *50*, 9429–9432; h) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Koehn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301; i) B. Chen, X. L. Hou, Y. X. Li, Y. D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671; j) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 483–486; *Angew. Chem. Int. Ed.* **2011**, *50*, 463–466; k) Y. Zhou, J. Zhao, L. Liu, *Angew. Chem.* **2009**, *121*, 7262–7264; *Angew. Chem. Int. Ed.* **2009**, *48*, 7126–7128; l) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593–1597; m) W. Yue, Y. Li, W. Jiang, Y. Zhen, Z. Wang, *Org. Lett.* **2009**, *11*, 5430–5433; n) J. M. Murphy, X.

Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434–15435.
[26] a) Z. Nowakowska, *Eur. J. Med. Chem.* **2007**, *42*, 125–137; b) C. B. Patil, S. K. Mahajan, S. A. Katti, *J. Pharm. Sci. Res.* **2009**, *1*, 11–22; c) J. R. Dimmock, D. W. Elias, M. A. Beazely, N. M. Kandepu, *Curr. Med. Chem.* **1999**, *6*, 1125–1150.
[27] a) L. Claisen, A. Claparede, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2460–2468; b) J. G. Schmidt, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1459–1461.
[28] a) S. Eddarir, N. Cotelle, Y. Bakkour, C. Rolando, *Tetrahedron Lett.* **2003**, *44*, 5359–5363; b) X.-F. Wu, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 5412–5416; *Angew. Chem. Int. Ed.* **2010**, *49*, 5284–5288; c) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 282–285; e) Y. Unoh, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2013**, *78*, 5096–5102; f) A. Bianco, C. Cavarischia, M. Guiso, *Eur. J. Org. Chem.* **2004**, 2894–2898.

