

Multicatalytic, asymmetric Michael/Stetter reaction of salicylaldehydes and activated alkynes

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We report the development of a multicatalytic, one-pot, asymmetric Michael/Stetter reaction between salicylaldehydes and electron-deficient alkynes. The cascade proceeds via amine-mediated Michael addition followed by an *N*-heterocyclic carbene-promoted intramolecular Stetter reaction. A variety of salicylaldehydes, doubly activated alkynes, and terminal, electrophilic allenes participate in a one-step or two-step protocol to give a variety of benzofuranone products in moderate to good yields and good to excellent enantioselectivities. The origin of enantioselectivity in the reaction is also explored; *E/Z* geometry of the reaction intermediate as well as the presence of catalytic amounts of catechol additive are found to influence reaction enantioselectivity.

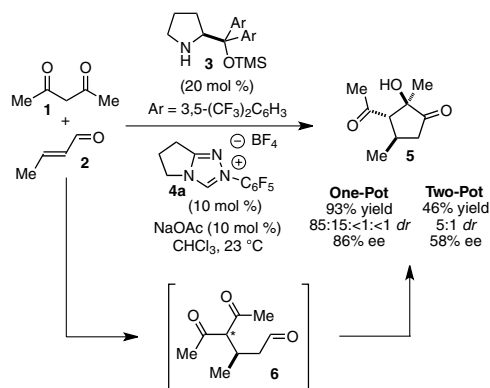
catalysis | organic synthesis | tandem catalysis

Cascade catalysis has garnered significant recent attention from the synthetic community as a means to swiftly assemble complex molecules from simple starting materials with minimal time, waste, and manipulation of reaction intermediates (1–11). Especially powerful in its application to total synthesis, asymmetric tandem catalysis has enabled rapid access to enantioenriched products with high levels of selectivity (1, 4–8, 10, 11). Although most examples exploit a single catalyst to promote multiple, sequential transformations (12–19), systems relying on two or more catalysts have been reported (2, 3, 11, 20). Inherent in any multiple catalyst system is the challenge of compatibility. Avoidance of mutual interference often obliges stepwise addition of catalysts or reagents and variation of reaction conditions over time (21–26). Nevertheless, cascades triggered by a single operation have been accomplished (20, 27, 28).

Very recently, we reported the development of a one-step, asymmetric Michael/benzoin reaction of β -ketoesters **1** and α,β -unsaturated aldehydes **2** mediated by compatible amine **3** and *N*-heterocyclic carbene (NHC) catalysts (Scheme 1) (29). Importantly, the one-pot procedure was found to give elaborated cyclopentanone products **5** in higher yield and enantioselectivity than a stepwise protocol, wherein intermediate aldehyde **6** is isolated and subjected to the benzoin reaction in a subsequent step (Scheme 1). This observation testifies to the power of cascade catalysis: By quickly relaying intermediates from one reaction to the next, catalysts can work synergistically to discourage undesired pathways.

Encouraged by the discovery that NHCs could participate in cascade catalysis, we were inspired to use NHCs to mediate the cascade assembly of benzofuranone products **9** asymmetrically (30). A range of biological activities associated with 3(2H)-benzofuranones including antifungal (31, 32), antipsychotic (33), and anticancer (34–36) properties make these products attractive synthetic targets. Among natural products containing a 2,2'-disubstituted benzofuranone core, rocaglamide demonstrates appreciable cytotoxicity in mice and human cells lines (37), vinigrol displays antihypertensive properties (38), and Sch202596 shows promise in Alzheimer's therapy (39).

Although a number of methods for the racemic assembly of benzofuranones containing C2 quaternary centers have been reported, many proceed from relatively advanced starting materials (40, 41) or suffer from competitive reaction pathways (42, 43). More rare are enantioselective preparations of 2,2'-disubstituted



Scheme 1. Multicatalytic Michael/Benzoin cascade.

benzofuranones. In 2008, Jørgensen and coworkers reported that 2-*tert*-butoxy carbonyl benzofuranone could be alkylated asymmetrically with tetraethyl ethylidene-bisphosphonate to give the corresponding 2,2'-disubstituted product in excellent enantioselectivity (44). In a different approach, we have shown that chiral triazolinyliene carbenes mediate the cyclization of aldehyde-tethered, β,β -disubstituted Michael acceptors related to **12** to give benzofuranone products in excellent enantioselectivities (Scheme 2) (45–47).

Although the strategies described provide benzofuranone products in good yield and exceptional selectivities, both make use of substrates that require multiple steps to prepare (47). We imagined that we could expedite the synthesis of benzofuranone products **9** by assembling intermediate aldehydes **12** in situ via a base-catalyzed conjugate addition reaction of salicylaldehydes **7** and electrophilic alkynes **8** (Scheme 2). Fan et al. have shown that 1,4-diazabicyclo[2.2.2]octane (DABCO) (**10**) efficiently mediates the addition of amine and oxygen nucleophiles to dimethyl acetylenedicarboxylate (DMAD) (**8a**) and alkyl propiolates (48, 49). In our envisioned sequence, a tertiary amine such as quinuclidine (**11**) or DABCO (**10**) activates alkyne **8** toward nucleophilic attack to give intermediate aldehyde **12** (Scheme 2). Subsequent chiral carbene-promoted Stetter reaction sets a quaternary stereocenter and yields product **9** asymmetrically.

Crucial to the success of any catalytic cascade is a compatible catalyst system. For many Stetter systems, tertiary amines perform as optimal bases for carbene generation (47, 50, 51). For

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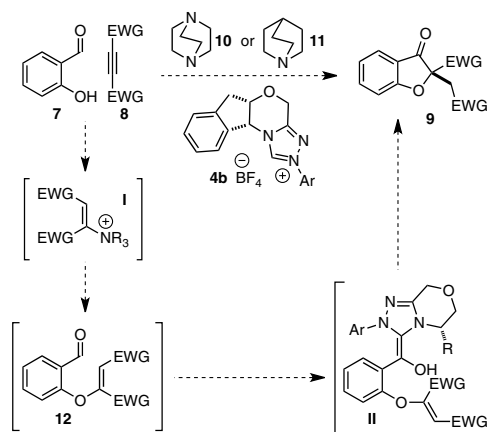
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Data deposition: The coordinates for the crystal structure of 9da have been deposited in the Cambridge Structural Database, Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/products/csd/, Cambridge CB2 1EZ, United Kingdom (CSD reference no. CCDC 783384).

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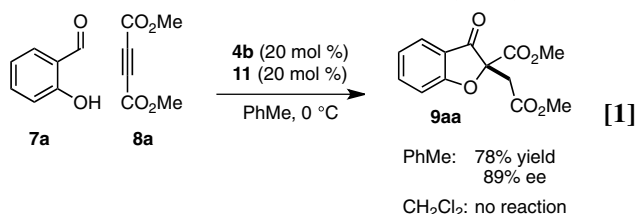
Scheme 2. Envisioned multicatalytic Michael/Stetter cascade.

this reason, we were encouraged that DABCO or quinuclidine would not only serve as nucleophilic “triggers” (48) to promote our imagined conjugate addition reaction but would also prove suitable bases to deprotonate triazolium salt precatalyst **4b** and generate the active carbene species.

Results and Discussion

We first examined whether our envisioned cascade could be performed in a one-pot, stepwise fashion. Carbenes have been shown capable of nucleophilic addition into DMAD and other activated alkynes (52, 53). To circumvent this undesired reaction pathway, a mixture of salicylaldehyde (**7a**) and DMAD (**8a**) was treated first with quinuclidine **11** and then with triazolium salt **4b**. Benzofuranone product **9aa** was isolated from this one-pot, two-step sequence in good overall yield and enantioselectivity (Table 1, entry 1). In a brief solvent screen, dichloromethane and 9:1 toluene/*t*-amyl alcohol provided product **9aa** in similarly high yields (Table 1, entries 1 and 4), whereas toluene gave the highest level of enantioselectivity (Table 1, entries 1–5). Lowering temperatures of the Stetter reaction improves enantioselectivity slightly but results in longer reaction times and lower product yields (Table 1, entries 6–8). No productive reaction is observed when the conjugate addition reaction is conducted at low temperatures (Table 1, entry 9).

Although we had developed conditions to mediate two bond-forming events in one reaction vessel with high levels of asymmetric induction, we hoped to reduce the number of required synthetic manipulations to a single operation. To this end, we treated a mixture of **7a**, **8a**, and **4b** with quinuclidine (**11**) at 0 °C in toluene. To our delight, the cascade proceeds smoothly to give **9aa** in undiminished yield and enantioselectivity (Eq. 1). The one-step protocol was found to be scalable: On a 1 g scale, product **9aa** (1.48 g, 79% yield) is obtained in 88% enantiomeric excess (ee). When the one-step reaction is performed in dichloromethane, however, only starting material and decomposition products are recovered; under these conditions, nucleophilic addition of **4b**-derived carbene into DMAD may interfere with the desired conjugate addition reaction (Eq. 1).



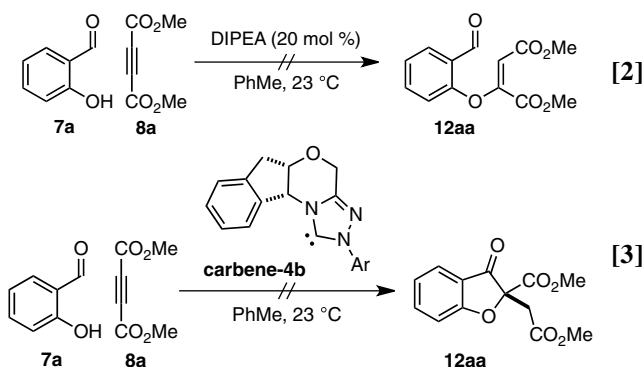
A series of control experiments were performed to probe the mechanism of the conjugate addition reaction. We had envisioned that Michael addition proceeds through nucleophilic activation of DMAD via intermediate **I** (Scheme 2). However, an

Table 1. Solvent and temperature screen

Entry	Solvent	T ₁ , °C	T ₂ , °C	Yield, %	ee, %
1	CH ₂ Cl ₂	23	0	85	81
2	THF	23	0	76	83
3	<i>t</i> -amyl alcohol	23	0	63	78
4	PhMe/ <i>t</i> -amyl alcohol (9:1)	23	0	87	86
5	PhMe	23	0	82	89
6	PhMe	23	23	75	86
7	PhMe	23	−10	60	90
8	PhMe	23	−40	64	92
9	PhMe	−40	NA	NR	NA

NA, not applicable; NR, no reaction.

alternative pathway could be imagined in which quinuclidine deprotonates salicylaldehyde, which adds conjugately to DMAD. To examine the viability of a base-catalyzed pathway, we exchanged quinuclidine for diisopropylethylamine. Treatment of salicylaldehyde and DMAD with this less competent nucleophile but similarly strong base resulted in complete recovery of starting material, suggesting that the proposed nucleophilic pathway is likely at work in our developed conditions (Eq. 2). Moreover, exposure of salicylaldehyde and DMAD to the free carbene derived from azolium salt **4b** gave no observable product by ¹H NMR spectroscopy (Eq. 3). It is highly probable that quinuclidine (**11**) rather than carbene-**4b** participates as the nucleophilic activator in our system.



With a productive one-step protocol in hand, we investigated the scope of the reaction with respect to salicylaldehyde **7**. Indeed, both electron-rich and electron-deficient salicylaldehydes with various substitution patterns participate in the Michael/Stetter sequence to give products **9** in good yields and moderate to excellent enantioselectivities (Table 2). Electron-deficient salicylaldehydes give generally higher enantioselectivities but poorer yields than electron-rich salicylaldehydes. The lower yields observed for these substrates are attributed to the competitive formation of chromene side products **13** derived from intramolecular aldol of intermediate enolate **III** (Eq. 4). Ortho-substituted salicylaldehydes give the lowest observed yields; steric bulk surrounding the phenoxide apparently impedes nucleophilic addition into DMAD (Table 2, entries 9–10). Indeed, when the 3-substituent is sufficiently large, no conjugate addition is observed (Table 2, entry 10). Absolute configuration of products **9** was assigned by X-ray crystal structure of iodide **9da**. The others were assigned by analogy.

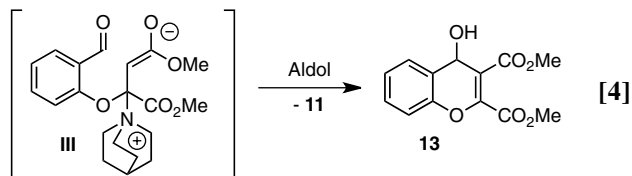


Table 2. Salicylaldehyde scope

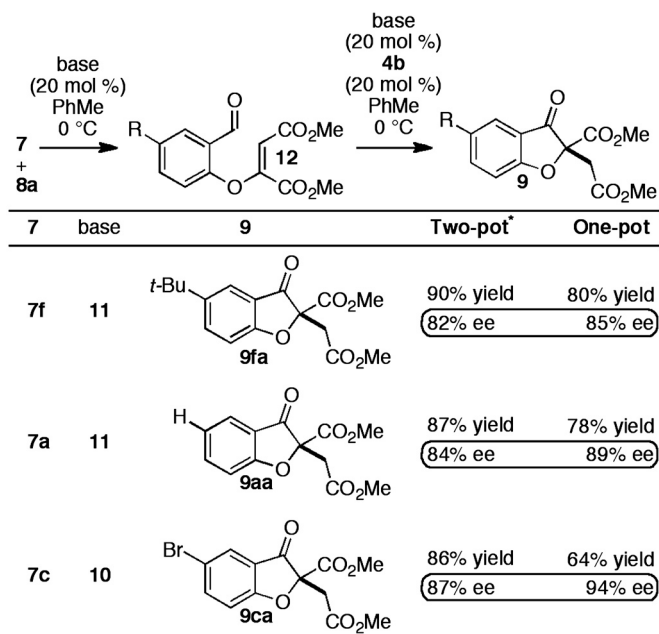
Entry	7	Base	Product (9)	Yield, %	ee, %
1	7a	11		78	89
2	7b	10		65	89
3	7c	10		64	94
4	7d	11		68	94
5	7e	11		77	86
6	7f	11		80	85
7	7g	10		66	86
8	7h	11		68	85
9	7i	10		62*	92
10	7j	11		NR	NA

NA, not applicable; NR, no reaction.

*9ja could not be separated from a minor impurity which coeluted in a variety of solvent systems.

We were intrigued by the variation of enantioselectivity across products **9** which appeared to be independent of steric or electronic factors. For example, 4- and 5-methoxy substrates **7h** and **7g** afford identical ees in spite of their differing electronic impact on both aldehyde and tethered alkene (Table 2, entry 7 vs. 8). Furthermore, sterically similar substrates **7d** and **7e** give products with widely disparate ees (Table 2, entry 4 vs. 5, 94% and 86% ee, respectively, corresponding to ~0.5 kcal/mol energy difference). To probe the origin of ee variation, we performed a two-pot Michael/Stetter protocol wherein intermediate aldehyde **12** was isolated and subjected to Stetter conditions. Treatment of DMAD and salicylaldehydes **7f**, **7a**, and **7c** with base gives the corresponding intermediate aldehydes **12fa**, **12aa**, and **12ca** in good yields (Scheme 3). When intermediate aldehydes **12fa**, **12aa**, and **12ca** are exposed to precatalyst **4b** and base in the usual manner, however, products **9fa**, **9aa**, and **9ca** are obtained in appreciably lower and more uniform enantioselectivities than those observed in the one-pot procedure (Scheme 3). We speculated that a trace impurity present in or side-product derived from certain salicylaldehydes **7** might be crucial for the high enantioselectivities obtained in the one-pot protocol; removal of the species during isolation of intermediate **12** would result in a drop in enantioselectivity of the subsequent Stetter reaction. Indeed, when the Stetter reactions of intermediate aldehydes **12ca** and **12fa** are conducted in the presence of an equivalent of exogenous salicylaldehyde **7c**, the high enantioselectivities of products **9ca** and **9fa** are recovered (Table 3, entries 1 and 2).

We aimed to identify the species present in exogenous salicylaldehydes **7** that might promote elevation of enantioselectivity. Strong H-bond donors such as catechols have been shown to improve yields and enantioselectivities of enamine-promoted Michael additions of aldehydes into enones (54–56). We hypothesized that trace catechol derived from Dakin-oxidation (57, 58) of salicylaldehyde might contribute to Stetter enantioselectivity. Addition of 10 mol % catechol **14a** to the Stetter reaction of intermediate aldehydes **12ca** and **12fa** improved product enantioselectivities to excellent 94% ee and 92% ee, respectively (Table 3, entries 3 and 4). When catechol **14a** is added with precatalyst **4b** in the one-pot, two-step protocol, similar improvement in enantioselectivity is observed for a variety of substrates

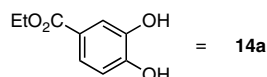


*Yield over two-steps

Scheme 3. Two-pot Michael/Stetter reaction.

Table 3. Additive effect on Stetter enantioselectivity

Entry	12	Base	Additive	Equiv	Yield, %	ee, %	
						W/o additive	W/additive
1	12ca	10	7c	1.05	78	86	93
2	12fa	11	7c	1.05	63	83	89
3	12ca	10	14a	0.1	90	86	94
4	12fa	11	14a	0.1	84	83	92

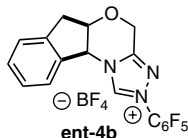
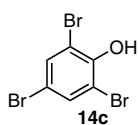
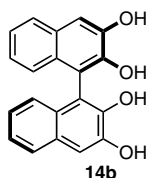


(Table 4, entries 1–3). Little change in selectivity is experienced in the one-pot, one-step procedure. Presumably, catechol **14a** adds conjugately to DMAD (**8a**) (48). Finally, an observed match/mismatch effect provides convincing support for catechol participation in the selectivity-determining step of the Stetter reaction. When chiral, binaphthyl-derived catechol **14b** is used as an additive, enantioselectivity of product **9aa** improves from 89% ee to 95% ee with (*S,R*)-precatalyst **4b** but shows no change with (*R,S*) precatalyst **ent-4b** (Table 4, entries 5 and 6). When catechol **14a** is substituted with acidic phenol **14c**, no improvement in enantioselectivity is observed (Table 4, entry 6).

Having explored the scope and selectivity of our Michael/Stetter reaction between DMAD and a variety of salicylaldehydes, we focused on incorporation of unsymmetrical alkynes as Michael acceptors in this cascade. Ketoalkynoates **8b** and **8c** participate in the one-step reaction with salicylaldehyde (**7a**) to give moderate yields of products **9ab** and **9ac** regioselectively but with low enantioselectivity (Table 5, entries 1 and 2). Attenuation of alkyne electrophilicity by substitution of the aryl ketone with phenethyl ketone **8d** improved the enantioselectivity of major product **9ad** (Table 5, entry 3), but resulted in formation of a second regioisomer **15ad** in ~10% yield (see *SI Text*). Interestingly, minor regio-

Table 4. Catechol effect on enantioselectivity in the one-pot, two-step Michael/Stetter reaction

Entry	7	Additive	4	Yield, %	ee, %	
					W/o additive	W/additive
1	7a	14a	4b	63	89	93
2	7f	14a	4b	78	85	90
3	7h	14a	4b	75	85	93
4	7a	14b	4b	63	89	95
5	7a	14b	ent-4b	73	-89	-89
6	7a	14c (1 equiv)	4b	60	89	89



somer **15ad** is obtained in high enantioselectivity (89%) relative to major product **9ad** (Table 5, entry 3). Phosphonate ester **8e** reacts in the one-pot, two-step protocol to give phosphonate **9ae** in fair yield and good enantioselectivity (Table 5, entry 4).

Although we were pleased to find that a number of unsymmetrical alkynes were tolerated in our one-pot protocol, we were interested in identifying substrates that would participate with high levels of both regioselectivity and enantioselectivity. Intermediate aldehydes **16a** containing a single electron-withdrawing substituent on the Michael acceptor have been shown to undergo the Stetter reaction with high enantioselectivity under conditions similar to these (Eq. 5) (47). Our initial attempt to access related intermediate aldehyde **16b** via the necessarily regioselective Michael addition of salicylaldehyde (**7a**) into alkynoate **17** resulted

Table 5. Unsymmetrical alkyne scope

Entry	Alkyne (9)	9:15*	Major product (9)
1		>20:1	9ab 60% yield 12% ee
2		>20:1	9ac 58% yield 18% ee
3		2.8:1	9ad 26% yield [†] 51% ee
4 [‡]		17:1	9ae 34% yield [§] 86% ee

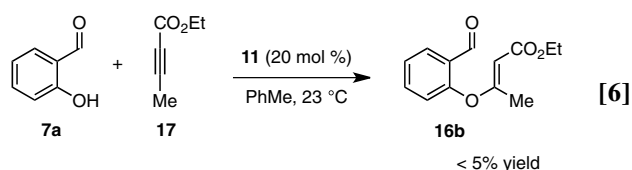
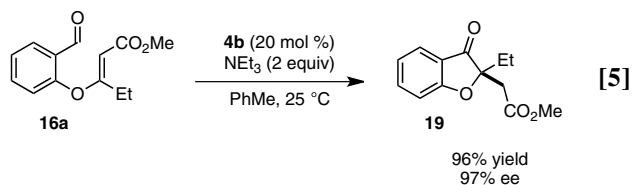
*Product ratios determined by ¹H NMR of the unpurified reaction mixture.
[†]Yield of **9ad** and **15ad** determined by ¹H NMR with reference to 2,6-Di-*tert*-butyl-4-methylphenol.

[‡]Phosphonate **9ae** was prepared according to the one-pot, two-step protocol (see *SI Text*).

[§]Phosphonate **9ae** could not be separated from a minor impurity which coeluted in multiple solvent systems.

only in isolation of starting material and decomposition products (Eq. 6) (59). Nevertheless, we were encouraged to try other modes of entry into **16b**. Shi and Shi have shown that activated allenes behave as alkyne surrogates in a DABCO-catalyzed conjugate addition reaction with salicylaldehyde (59). Indeed, we were delighted to find that subjection of allenone **18a** and allenolate **18b** to our one-pot, two-step protocol in a variety of solvents gave benzofuranone products **19a** and **19b** in moderate yields and good to excellent enantioselectivities (Table 6).

•Previous Work (ref. 47)

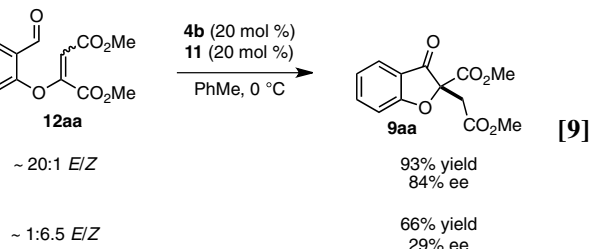
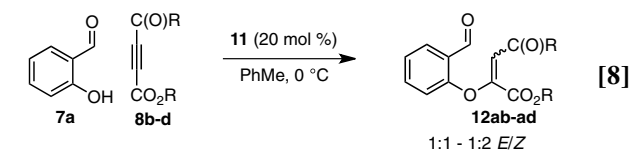
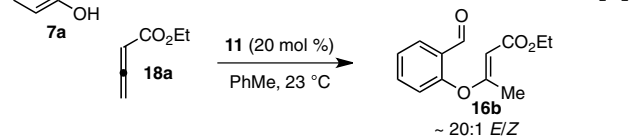
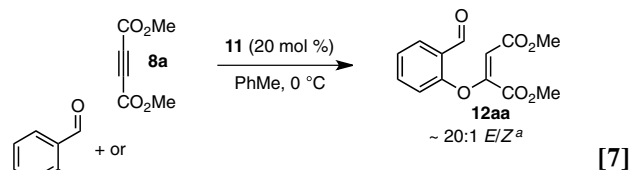


We hoped to understand why certain substrates (DMAD, allenolate **18b**) react with much greater enantioselectivity than others (ketoalkynoates **8b** and **8c**). A factor that has been shown to influence Stetter enantioselectivity is olefin geometry (46, 47). Although intermediate aldehydes **12aa** and **16b** derived from DMAD and allenolate **18b** form with near perfect *E*-selectivity under our conditions (Eq. 7), intermediate aldehydes derived from ketoalkynoate substrates (**8b-d**) are observed as unselective mixtures of *E/Z* isomers (Eq. 8). For a number of Stetter scaffolds, the *E*-isomer has been shown to react in higher yield and with greater enantioselectivity than the corresponding *Z*-isomer (46, 47). To examine whether a relatively high *Z/E* ratio could contribute to the low enantioselectivities obtained for ketoalkynoate substrates **8a-c**, we subjected a 6.5:1 *Z/E* mixture (60) of intermediate aldehyde **12aa** to our established Stetter conditions. Whereas *E* isomer **12aa** reacts to afford product **9aa** in 84% ee, *Z*-enriched **12aa** gives **9aa** in only 29% ee and in appreciably lower yield (Eq. 9). The disparity in enantioselectivity across batches of intermediate aldehyde **12aa** reinforces previous observations that

Table 6. One-pot, two-step Michael/Stetter reaction with activated allenes

Entry	18	Solvent	T ₁ , °C	T ₂ , °C	Product (19)	Yield, %	ee, %
1	18a	THF	23	0	19a	60	78
2	18b	PhMe	23	23	19b	50	98
3	18b	PhMe	110	110	19b	50	89
4	18b	CH ₂ Cl ₂	23	23	19b	59	96

olefin geometry contributes significantly to Stetter selectivity.



Influence of olefin geometry on Stetter enantioselectivity (^a*E/Z* ratios determined by ¹H NMR).

In summary, we have described a unique and scalable one-pot procedure for the highly enantioselective preparation of benzofuranone products in moderate yields from simple starting materials. We have demonstrated that the one-pot Michael/Stetter protocol is superior to the two-step procedure with respect to enantioselectivity, and we have expanded on this observation to show that catechol additives improve enantioselectivity in the context of both two-pot and one-pot, two-step reactions. Moreover, we have identified olefin geometry as an important factor influencing Stetter enantioselectivity. Finally, we have illustrated that activated allenes behave as competent, *E/Z*-selective Michael acceptors in our one-pot, two-step reaction to provide access to alkyl-substituted benzofuranones **19** in moderate to excellent enantioselectivities. Investigations aimed at generalizing this concept are currently underway.

Materials and Methods

General methods, detailed experimental procedures, and characterization data for the compounds described in this article can be found in the *SI Text*, which is available free of charge on the PNAS web site.

General Procedure for the Multicatalytic Michael/Stetter Reaction. A 1-dram vial was equipped with a magnetic stir bar under argon and charged sequentially with DMAD (**8a**) (21 mg, 0.15 mmol), salicylaldehyde **7** (0.16 mmol), and triazolium salt **4b** (14 mg, 0.030 mmol). Toluene (1.5 mL) was added, and the mixture was cooled to 0 °C. Quinuclidine (**11**) (3.0 mg, 0.030 mmol) or DABCO (**10**) (3.0 mg, 0.030 mmol) was added in one portion, and the reaction was monitored by TLC (hexanes/acetone). When the reaction was judged to be complete, the mixture was quenched with glacial acetic acid (1–2 drops), filtered through a plug of silica with Et₂O (~40 mL), and concentrated in vacuo. The resulting product **9** was purified via flash chromatography.

Procedure for the Preparation of 9aa on 7.0 mmol Scale. A 250-mL, flame-dried, round-bottom flask was charged with triazolium salt **4b** (164 mg, 0.350 mmol) and evacuated for 3 min, then filled with argon. After the evacuation procedure was repeated an additional two times, DMAD (**8a**) (1.01 g, 7.12 mmol), salicylaldehyde (**7a**) (933 mg, 7.64 mg), and toluene (72 mL) were added sequentially, and the reaction mixture was cooled to 0 °C. Quinuclidine

(11) (156 mg, 1.40 mmol) was added portionwise to the reaction mixture. After it was allowed to stir at 0 °C for 9 h, the reaction was quenched with glacial acetic acid (150 μ L) and poured directly onto a silica gel column (5:1 – 1:1 hexanes/EtOAc) to give 1.48 g (79% yield) of **9aa** as a clear, amorphous solid.

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