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Relay Catalysis To Synthesize β-Substituted Enones: Organocatalytic Substitution of Vinylogous Esters and Amides with Organoboronates

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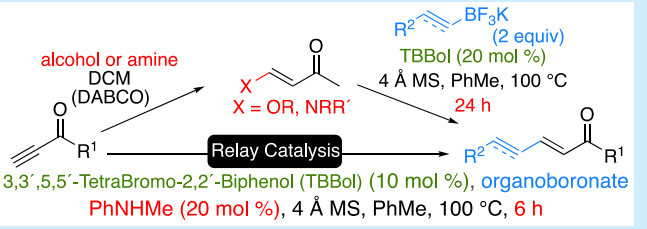
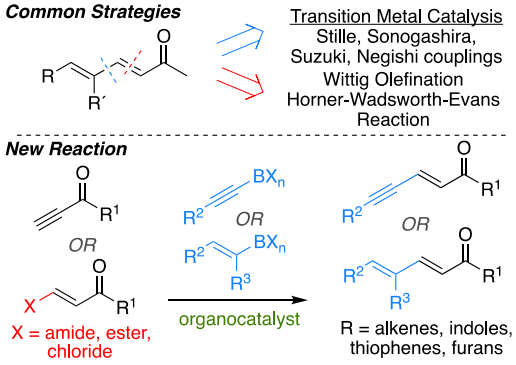
ABSTRACT: Organocatalysis was shown to facilitate conjugate additions to vinylogous esters and amides for the first time. Subsequent elimination of a β-alcohol or amine provided π-conjugated β-substituted enones. Remarkably, nucleophile addition to the electron-rich vinylogous substrates is more rapid than classical enones, forming monosubstituted products. A doubly organocatalytic (organic diol and methyl aniline) conjugate addition synthesized the products directly from alkynyl ketones. Both of these catalytic transformations are orthogonal to transition metal catalysis, allowing for good yields, easily accessible or commercially available reagents, high selectivity, reagent recovery and recyclability, facile scalability, and exceptional functional group tolerance.



Polyenes occur in natural products[1] and can be used in Nazarov reactions to build larger, more complex structures.[2] Transition metal cross-couplings and carbonyl olefinations to form polyenes are powerful and well developed (Scheme 1) but nonetheless suffer from limited functional group tolerance, harsh conditions, difficulty in catalyst recovery, cost, toxicity, and/or environmental issues on scale up in industrial applications.[3] Conjugate addition reactions effectively build structural complexity in challenging molecules.[4] This report details organodiol catalysis with organoboronate nucleophiles for 1,4-additions to vinylogous amides and esters, as well as relay catalysis with this newly discovered reactivity to form polyenes directly from abundant alkynyl ketones. Both catalytic species are readily recycled, and this coupling strategy is highly functional group tolerant and transition metal free.

Scheme 1. Strategies for Polyene Structures



The conjugate addition of organoboronates to enones was first reported by Suzuki,[5] followed by enantioselective versions,[6] and a significant advance to broaden the range of nucleophiles used trifluoroborate salts.[7] Kinetic studies suggested that the reaction rate is increased by electron-rich β-substituents that stabilize developing cationic charge at the β-carbon.[8] In light of that observation, we hypothesized that resonance electron donor substituents, ethers and amines, would make the enone even more reactive.[9,10] This paradigm would reverse that of nearly all conjugate addition reactions, for which vinylogous esters and amides are too electron-rich to be competent substrates.[11] Precedence for such conjugate additions is limited to a few reports of palladium catalysis to add aryl boronic acids to vinylogous amides.[12] In a single report of vinylogous substitution, monoaddition did not occur since the enone from the first conjugate addition was more electron-deficient and therefore more reactive than the vinylogous amide. Moreover, limited functional group tolerance was demonstrated.

We tested the hypothesized conjugate addition to vinylogous esters with a 3,3′- modified BINOL catalyst (Table 1, entry 1) that was previously reported to catalyze 1,4-additions.[7,8] The resulting 2,4-dienyl ketone was confirmed to be the linearly conjugated polyunsaturated ketone **3**, the result of the anticipated 1,4-addition of the BF_3K salt followed by phenoxide

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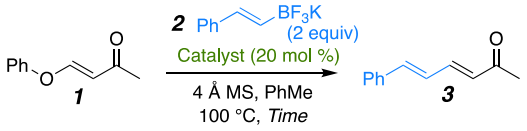
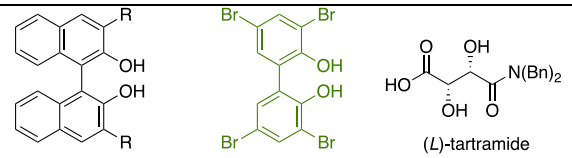
Table 1. Catalyst Screen



entry	catalyst	time	yield
1	(±)-C_7F_7 BINOL	24 hours	86[b]
2	(±)-IODO BINOL	24 hours	85[a]
3	(±)-BINOL	24 hours	81[b]
4	2,2′-biphenol	48 hours	82[b]
5	TBBol	18 hours	82[b]
6	(*L*)-tartaric acid	72 hours	77[a]
7	(*L*)-tartramide	48 hours	6[a]
8	1,4-butanediol	48 hours	42[a]
9	none	48 hours	61[a]

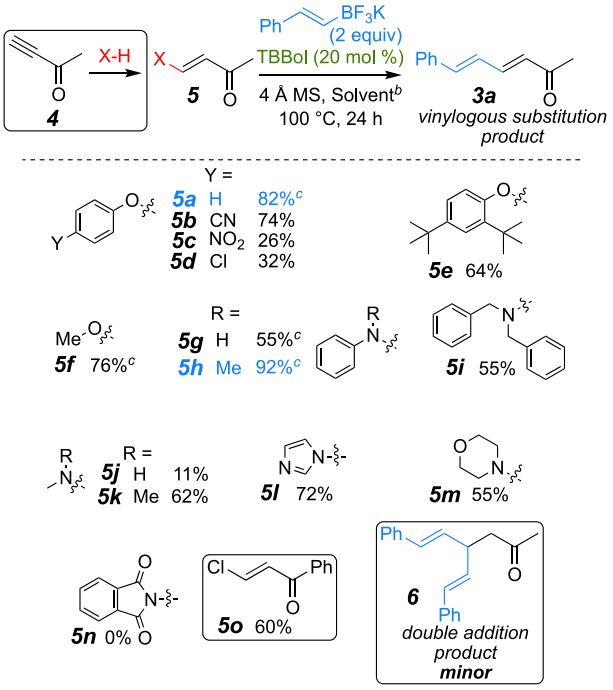


[a]Based on quantified peak area in the ^{1}HNMR of the crude reaction material relative to 4-methylnitrobenzoate as an internal standard. [b]Isolated yields, average of three trials.

elimination to give exclusively the *trans*-alkene. As this substitution produced an achiral product, a catalyst screen was performed using racemic and achiral organic diols, including unmodified BINOL and 2,2′-biphenol (entries 3 and 4). The less reactive biphenol could be improved by one-step bromination to give **T**etra**B**romo**B**iphen**ol** (TBBol),[13] which is consistent with the established need for electron-poor biaryl diols for effective catalysis.[6,14] A tartramide that was reported for use with organoboronate esters[15] was tested, but it did not provide useful yields (entry 7). Neither Lewis acid nor Lewis base additives increased catalytic activity, and stronger acids or bases decomposed the vinylogous ester and amide substrates. For most additives, yields were lowered.[17]

To assess the leaving group impact, myriad vinylogous amides and esters, as well as a *β*-chloroenone, were examined. These substrates were commercially available or easily accessible from 3-butyn-2-one (**4**) (Scheme 2).[16] Vinylogous esters gave fair to good yields of the polyene, with 4-phenoxy-but-3-en-2-one (**5a**) providing the highest yield at 82%. Yields from tertiary vinylogous amides were comparable to those from vinylogous esters, with the highest at 92% from the methyl-phenyl amide **5h**. Primary amine leaving groups gave decreased yields, likely due to liberated amine catalyzing side reactions. In each case, no conjugate addition without *β*-elimination was observed, and all esters and amides screened provided polyene **3**. The only other identifiable product from these reactions was a symmetric doubly *β*-substituted ketone (i.e., **6**), the result of a significantly slower second conjugate addition. It is unusual for the more electron-rich vinylogous substrate to undergo nucleophilic addition faster than the relatively electron-poor enone product. Thus, the diol-catalyzed reaction showed inverted reactivity relative to Pd.[12]

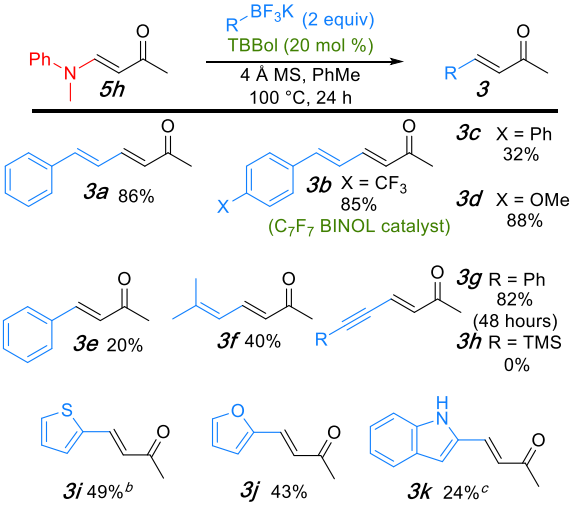
Scheme 2. Evaluation of Vinylogous Esters and Amides[a]



[a]Yields of **3a** from **5** based on quantified peak area in the ^{1}HNMR of crude reaction material relative to 4-methylnitrobenzoate as an internal standard. [b]Toluene was the solvent for the amides and vinyl chloride. For the esters, the solvent was 1,4-dioxane.[17] [c]Average isolated yield of **3a** from **5** from three experiments.

Diverse organoboronate nucleophiles were useful, including the often-sensitive alkyne salts (Scheme 3). Boronic acids were

Scheme 3. Nucleophiles for the Monocatalytic Reaction[a]



[a]Isolated yields. [b]Boronic acid used. [c]Boc-indole-2-BF_3K used.

also active, though they exhibited slower reactivity that could be compensated for by increasing reaction time.[17,18] Substitution of the styrenyl aryl ring did not considerably affect yields except for a *para*-phenyl (**3c**). Aromatic nucleophiles (**3e**, **3i**, **3j**, **3k**) gave decreased yields, likely due to the necessity of dearomatization during the key C−C bond formation. Alkyne nucleophiles (**3g**) were reactive, but required increased reaction times. Unsub-

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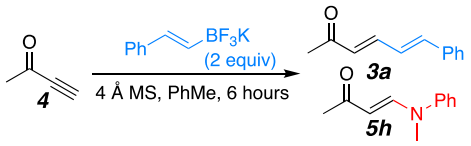
stituted or TMS alkynyl boronates (**3h**) performed poorly, perhaps due to conflicting reactivity.

Synthesizing vinylogous esters and amides that varied the ketone substituent experienced low yields (see Supporting Information (SI)), even with excess amine or catalysts like DABCO. Additionally, alkyne **4** was not reactive to organoborates under any conjugate addition conditions, which was disappointing since that reaction would have directly generated the doubly unsaturated ketones **3**.

To overcome these limitations, we envisioned a doubly catalytic reaction to both form the vinylogous ester or amide and perform the vinylogous substitution in the same reaction by generating small amounts of the vinylogous intermediate in situ (Scheme 5). This would avoid purifying potentially unstable vinylogous esters and amides. Mechanistically, methyl aniline would add to alkynyl ketone **4** to form vinylogous amide **5c**, which would then be reactive for the conjugate addition catalyzed by the organodiol. After complexation of the organoboronates **2** to TBBol,[7] Lewis base coordination provides **II**. Bond formation proceeds to give the boron enolate **IV**,[6,14] and β-elimination of the aniline would form the polyene **3a**. This C−C bond formation has interesting elements of both conjugate addition and Petasis mechanisms, the latter relationship being apparent from resonance structure **IIb**. A possible reason for only dienyl ketone **3a** being observed could be intramolecular Lewis acid complexation as shown in **IV** followed by concomitant β-elimination/deborylation to generate borate **V**. Catalyst exchange could then occur to regenerate the aniline and the organodiol.

The two best leaving groups (phenol and methyl aniline) were tested, and polyene **3a** was formed in 27% yield with 1 equiv of methyl aniline and 20 mol % TBBol. No **3a** was observed with phenol. Reaction improvement increased the yield of **3a** to 96% in less time than those with pure vinylogous esters and amides (6 h instead of 24 h, Table 2, entry 1) using a substoichiometric quantity of methyl aniline.[17] No product was observed without aniline, confirming the necessity of an intermediary vinylogous amide (entries 2, 4, 6, 7, and 9). Without TBBol, slow product formation occurred if aniline were present (entry 3), which is consistent with the observed background reaction (Table 1, entry 9). TBBol increased product formation substantially (compare Table 2, entries 1 and 3). Phosphine decreased the formation of both vinylogous amide **5g** and ketone **3a** (entry 8), and DABCO suppressed organoborate addition entirely. These controls are consistent with the mechanism in Scheme 4 and exclude Bayless−Hillman-like C−C bond formation.

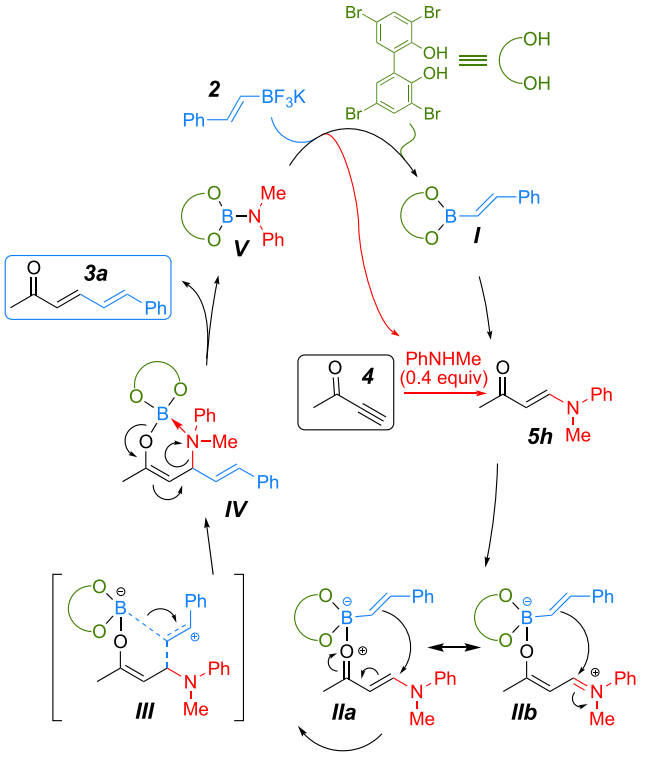
Table 2. Relay Catalysis Control Experiments



entry	TBBol	PhNHMe	Additive (40 mol %)	yield **3a** (%)[a]	yield **5g** (%)[a]
1	20 mol %	40 mol %	none	96	0
2	20 mol %	none	none	0	0
3	none	40 mol %	none	31	30
4	20 mol %	none	DABCO	0	0
5	none	40 mol %	DABCO	0	31
6	none	none	DABCO	0	0
7	20 mol %	none	PBu_3	0	0
8	none	40 mol %	PBu_3	19	13
9	none	none	PBu_3	0	0

[a]Based on quantified peak area in the ^{1}HNMR of the crude reaction material relative to 4-methylnitrobenzoate as an internal standard.

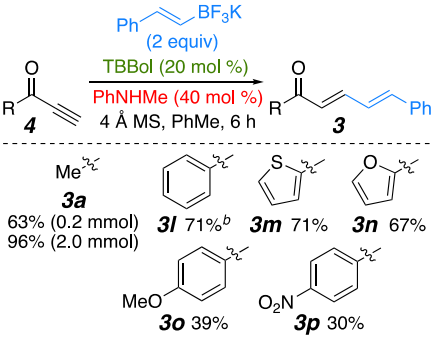
Scheme 4. Catalytic Cycle



The doubly catalytic reaction also had greater tolerance to ketone modifications. As hypothesized, the vinylogous esters and amides that had been problematic were made productive (Scheme 5). Ketone aryl substituents (**3o** and **3p**) gave lower yields than methyl substitution (**3a**), but heterocycle substituents reacted similarly to a methyl substituent (see **3m** and **3n**).

Relay catalysis allowed a significant variety of nucleophiles to add to alkynyl ketones (Scheme 6). In this process, boronic acids performed almost as well as trifluoroborate salts (see SI). Aryl trifluoroborates were not as reactive, presumably due to the need to break aromaticity in C−C bond formation (i.e., **II** to **III**,

Scheme 5. Doubly Catalytic Trials[a]



[a]Isolated yields. [b]24 h.

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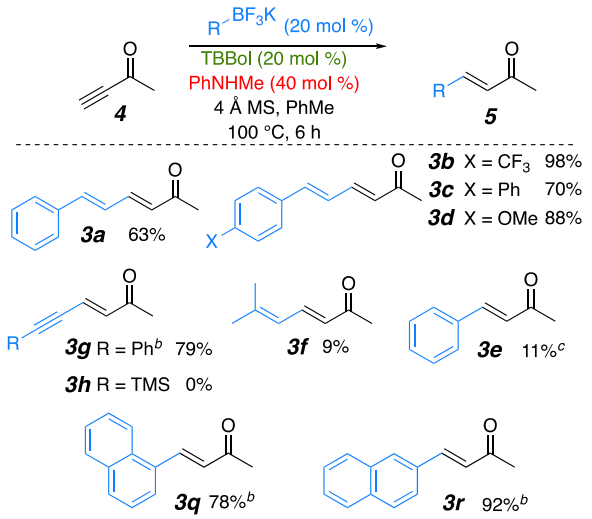
Scheme 6. Nucleophile Variation with Relay Catalysis[a]

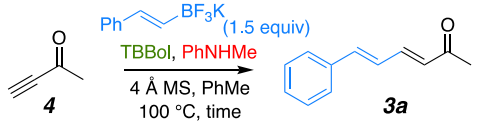


[a]Isolated yields. [b]Reaction time 48 h. [c]1 equiv of LiBr for 6 h.

Scheme 4), but almost all vinyl and some alkynyl trifluoroborates gave good yields. This was supported by the observation that naphthyl nucleophiles, which have less aromatic stabilization, produced higher yields.[7] Aryl substitution for styrenyl nucleophiles did not significantly affect yields (**3b**–**3d**). Yields could be increased by individual optimization; for example, increasing the reaction time to 48 h increased the yield for **3g**. Lithium bromide, previously used in conjugate additions with aromatic nucleophiles, allowed formation of the *β*-phenylenone **3e**. The only example that performed worse in the relay catalysis was diene **3f**. Generally, the strength of this method lies in accommodating heterocycles, alkynes, and other sensitive functional groups that are problematic for other strategies. Functional group tolerance was assessed as described by Glorius,[19] showing high tolerance in nearly all cases.[17] Though a few functional groups were less tolerant of elevated temperatures, this reaction experiences only minor reductions in yield when the temperature is decreased as low as 50 °C, so thermally sensitive groups could be preserved with an increase in reaction time.[17]

This transformation excelled on a larger scale, with a nearly quantitative yield on a 2 mmol scale (Table 3, entry 1). We note that the conditions reported in Scheme 6 were broadly applicable for a successful reaction. Table 3 demonstrates that, for an individual substrate reaction, optimization allows for low catalyst loadings while maintaining high yields. With adjustments to concentration and reaction time, lower catalyst loadings could be used with minimal loss in yield (entry 5). TBBol and most of the methyl aniline are easily recoverable upon purification, allowing for recycling.

Table 3. Scale up and Optimization of a Specific Substrate

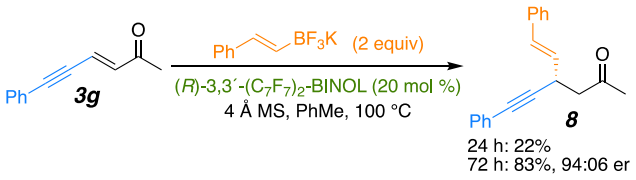


entry	scale	TBBol loading	PhNHMe loading	concn	time	yield[a]
1	2 mmol	20 mol %	40 mol %	0.1 M	6 h	95%
2	2 mmol	10 mol %	10 mol %	0.5 M	14 h	60%
3	2 mmol	5 mol %	5 mol %	0.5 M	14 h	49%
4	5 mmol	10 mol %	20 mol %	0.5 M	6 h	55%
5	5 mmol	10 mol %	20 mol %	0.5 M	42 h	88%

[a]Isolated yields.

Products like alkynyl enones **3g** can be difficult to reliably access and control, which is likely why there have only been three reports of their use for enantioselective conjugate additions.[20] We found that these compounds could be enantioselectively transformed into *β*-branched ketones by subsequently using a chiral diol catalyst (Scheme 7). Although

Scheme 7. Enantioenriched Double Addition Products



3g was formed in only 6 h from the alkynyl ketone (Scheme 6) or 48 h from the vinylogous amide (Scheme 3), the addition of the second nucleophile to give **8** required 3 days for high conversion with 96:4 er. This comparison clearly demonstrated the greater reaction completion time for enones relative to vinylogous amides. To our knowledge, there are no enantioselective reports for the formation of *β*-alkynyl/*β*-alkenyl ketones.

In conclusion, a previously inaccessible conjugate addition reaction has been formulated, and we present the first report of organocatalyzed vinylogous substitution of vinylogous amides and esters to provide conjugated *β*-substituted enones. We have exploited this reactivity for relay catalysis to use propargyl ketones directly. These transformations are catalyzed by an easily accessed brominated biphenol organocatalyst, TBBol. The organodiol and trifluoroborate nucleophiles perform the equivalent transformation as transition metal cross-couplings, but with increased functional group tolerance as proven by a Glorius-inspired study. This method allows inclusion of a variety of unsaturated substituents, including heteroaromatics and alkynes. We are now applying this methodology to the synthesis of more complex structures and of cross-conjugated organic polymers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04584.

Experimental details and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Occasionally, base catalysis with DABCO is necessary for the formation of the vinylogous ester or amide. DABCO increases the rate of reaction in most cases.
(16) For substrate synthesis, full experimental details, compound characterization, and control experiments, see Supporting Information.
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