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The Ketene-Surrogate Coupling: Catalytic Conversion of Aryl Iodides to Aryl Ketenes via Ynol Ethers**

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Abstract

tert-Butoxyacetylene is shown to undergo Sonogashira coupling with aryl iodides to yield aryl-substituted tert-butyl ynol ethers. These intermediates participate in a [1,5]-hydride shift, which results in the extrusion of isobutylene and the generation of aryl ketenes. The ketenes are trapped in situ with multiple nucleophiles or undergoelectrocyclic ring closure to yield hydroxynaphthalenes and quinolines.

Keywords

Ketene; Sonogashira coupling; naphthol; ynol

Benzyl ketones and aryl acetic acid derivatives are found in many biologically active natural products anddrug candidates (Scheme 1). For example, benzyl ketones or their derivatives appear within actinoplanone A, the epilepsy drug oxcarbazepine, and the platelet inhibitor prasugrel. Likewise, aryl acetic acid derivatives appear in many natural products and pharmaceutical agents, such as (−)-curvularin and penicillin G. For these reasons, we were motivated to develop a mild and generalcatalytic method to access these substructures. Herein we report a novel cross coupling between aryl iodides and ynol ethers that yields aryl ketenes (**1**) and therefore provides a general catalytic synthesis of benzyl carbonyl compounds.

Previous catalytic approaches to aryl acetic acid derivatives have relied on arylation of enolates. Ni and Pd catalyze couplings of esters and amides with aryl halides. These protocols have proven relatively general, and, in some cases, enantioselective.[1] Nonetheless, enolate couplings require strongly basic conditions, elevated temperatures and/or independent preparation of the zinc enolates. They frequently involve specialized ligands, and achieving selective mono-arylation can be challenging. Alternative catalytic approaches to the α-arylation of carbonyl compounds include α -arylation with iodonium salts[2] or

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activated sulfoxides,[3] addition of aldehydes to *in situ*-generated quinone derivatives,[4] and a recent oxidative coupling of ketones with nitroarenes.[5]

We hypothesized that aryl ketenes (**1**) could give rise to esters, amides, carboxylic acids, ketones and thioesters from the same intermediate. In contrast, the alternative approaches outlined above require separate reaction conditions for each of these products, if they are accessible at all. To date, no direct methods have been reported to couple metalated ketene (**2**) with an aromatic ring, and such a reaction appeared implausible. An alternative presented itself, however, in the [1,5]-hydride shift of ynol ethers. This process is accompanied by the sigmatropic extrusion of an olefin, and occurs under thermal conditions.[6] Finally, the requisite aryl-substituted ynol ethers (**3**) could arise from the currently unknown coupling of an alkoxyacetylene with aryl halides. In this way, an alkoxyacetylene could serve as a ketene surrogate, so we refer to the process as the ketene surrogate coupling.[7,8]

Thermal generation of ketenes from ynol ethers has been exploited previously in the synthesis of complex molecules, which indicates that this transformation is reliable and occurs under mild conditions.[9] In contrast, the cross coupling of alkoxyacetylenes remains poorly developed. In this context, Stille coupling of alkoxyethynyltin reagents has been described,[10] but Sonogashira coupling could directly connect the aryl iodides and ynol ethers without necessitating pre-functionalization of the acetylene motif. While the Sonogashira coupling between menthol-derived ynol ethers and terminal vinyl iodides has been investigated,[11] the only Sonogoshara coupling between an ynol ether and an aryl halide of which we are aware proceeded in only 11% yield.[12,13]

To develop the ketene surrogate coupling, we first investigated the Pd-catalyzed coupling of alkyl ynol ethers with aryl iodides. 4-Cyano-iodobenzene **4a** was combined with ethoxy acetylene, $Pd(PPh_3)_4$ and CuI in triethyl amine (entry 1). No desired product was isolated, and the alkyne appeared to have polymerized under the reaction conditions. Reasoning that a more sterically hindered alkyne might be less prone to polymerization, we repeated the experiment using *tert*-butoxy acetylene.[14] In addition to being more stable, *tert*-butoxyacetylenes rearrange to ketenes at around 80 °C compared to the 120 °C that is required for conversion of ethoxyacetylenes to ketenes.[15] We were encouraged when alkyne **5a** was formed in 54% yield when *tert*-butoxyacetylene was used (entry 2). The reaction also generated products arising from hydration and hydrolysis of **5a** (**6a** and **7a**, respectively) and enyne **8a**, a 2:1 adduct of *tert*-butoxy acetylene and the aryl iodide.

To minimize the formation of ester and carboxylic acid side products, we included molecular sieves in the reaction. Additionally, the use of a bulkier base, $^{i}Pr_2NEt$, suppressed the generation of enynol ether **8a** (entry 3). Under these conditions, the aryl-substituted ynol ether **5a** was formed in an improved 85% yield. Enynol **8a** could arise from either dimerization of *tert*-butoxyacetylene followed by coupling with the aryl iodide or carbometalation of the Sonogashira product **5a**. We favor the former hypothesis because *tert*-buytoxyacetylene did not add to isolated ynol ether **5a** under the reaction conditions We speculate that a bulky amine prevents the $(R_3N)_nCu$(acetylide) complex from reacting with a

second equivalent of *tert*-butoxyacetylene. Ultimately, the reproducibility of the reaction could be improved by forming $Pd(PPh_3)_n$ *in situ* from $Pd_2(dba)_3$ and PPh_3 (entry 4).[16]

Unfortunately, when these conditions were applied to an electron neutral substrate (**4b**), incomplete conversion was observed (entry 5). Changing to a secondary amine ($^iPr_2NH$) accelerated the coupling (entry 5) without introducing impurities. Under these conditions, aryl iodide **4b** was completely consumed, and the aryl-substituted ynol ether **5b** was formed in good yield (entry 6). Reactions with $^iPr_2NH$ are generally faster than those containing iPr_2NEt, but electron-poor arenes form small quantities of the corresponding tertiary amide (e.g. **9a**) during the reaction. Accordingly, we generally recommend $^iPr_2NEt$ for electron poor substrates and $^iPr_2NH$ for electron rich and neutral substrates. Finally, sterically hindered substrates such as **4c** benefited from an even more active catalyst. In particular, tri(2-furyl)phosphine (TFP) formed a competent catalyst in conjunction with $Pd_2(dba)_3$, promoting the coupling of a hindered aryl iodide in good yield (entry 8). To summarize, three closely related reaction conditions accommodate a wide variety of substrate classes: the couplings are usually more efficient with $^iPr_2NH$ than with $^iPr_2NEt$, although with electron deficient substrates, we observed minor amounts of the amide 9 when $^iPr_2NH$ was used. While these substrates perform admirably with inexpensive PPh_3, challenging aryl iodides often necessitate the electron deficient phosphine TFP.

The coupling tolerates a wide range of electronic properties and functional groups (Table 2). In these experiments, Cu, Pd, and amines were removed by rapid chromatography over neutral Al_2O_3. In general, electron neutral or electron rich Sonogashira products could be isolated in high purity whereas electron poor congeners were prone to hydrolysis. For example, the ynol derived from 4-methyoxy-iodobenzene was stored for >1 year at 4 °C with no signs of decomposition. In contrast, the *p*-CN-substituted ynol **5a** underwent hydrolysis to the extent of 5–10% upon attempted purification. Therefore, following filtration over Al_2O_3, the crude aryl-substituted ynol ethers **5** were heated in the presence of morpholine to generate, consecutively, the aryl ketene (1) and then the morpholine amides (10, Table 2).[17] These amides were targeted because of their utility in the synthesis of ketones (see below). They behave similarly to Weinreb amides, but are more stable and less expensive.[18] We found that ketones, esters, and nitro, cyano and trifluoromethyl groups were all compatible with the reaction conditions. Likewise, substrates featuring electron donating groups including 2-, 3- and 4-methyl (**10q**, **10r**, **10h**) and 2-, 3- and 4-methoxy (**10s**, **10t**, **10k**) provided the corresponding morpholine amides in good yield. Both 1- and 2-iodonaphthalene were excellent substrates (**10v**, **10m**). Moreover, several heterocycles participated in the reaction yielding 3- and 4-substituted pyridines (**10n**, **10o**) and 5- and 7-substitued indoles (**10p**, **10w**). In the latter cases, the indole NH did not require protection. The thiazole **10x** was formed in good yield, extending the chemistry to 5-membered heterocycles. Aryl bromides do not couple efficiently, but this characteristic allows for the selective coupling of 4-bromo-iodobenzene to form the 4-bromophenyl acetamide **10j** in 74% yield. Additionally 4-fluoro-iodobenzene provided **10c** in poor yield due to volatility of the ynol ether and instability of the amide.

The examples in Table 2 involve trapping the arylketene with morpholine, but we wanted to explore the reactivity of this intermediate more broadly. To this end, ynol ether **5g** was

synthesized on a 2.9 g scale and isolated in 88% yield (Scheme 2). Ketene **1g** was then generated at 75 °C in the presence of a variety of trapping reagents. Oxygen-based nucleophiles reacted cleanly and efficiently. Specifically, water, methanol, and primary, secondary and tertiary alcohols yielded the carboxylic acid or esters **11a–11e** in high yield. Likewise, pentafluorophenol and phenol formed the phenolic esters **11f** and **11g**. The former could serve as a useful acylating agent while the latter can participate in a Fries rearrangement (see below). In the special case of allyl alcohol, the intermediate allyl ester was exposed to soft enolization conditions to promote a Claisen rearrangement in a two-step, one pot procedure to give *C*-allyl ester **12**.[19] In related transformations, amines other than morpholine react with equal facility. Thus, Weinreb amides (**13**) emerge from trapping with (MeO)MeNH, most conveniently free-based *in situ* from the hydrochloride salt, and aniline reacted to form anilide **14** in nearly quantitative yield. Of note, HI and isobutylene are the only chemical waste products generated in these acylations.

We next explored strategies to form ketones through C-C bond formation. To this end, ynol **5g** was heated in the presence of the ylide derived from ethyl 2-bromopropionate (**15**), and the trisubstituted allene **16** was isolated in good yield.[20] Similarly, exposure to alkyl-vinyl ethers initiated a [2+2]-cycloaddition to provide the cyclobutanone products **17** as single trans diastereomers.[21] These last examples provide compelling evidence for the intermediacy of ketene **1g**. While, in principle, most of the other products in Scheme 2 could have arisen from Nu-H addition across the ynol ether triple bond followed by hydrolysis of the *tert*-butyl enol ether, the formation of allenes and [2+2] adducts is more consistent with a ketene intermediate under these reaction conditions.

The facile synthesis of a variety of aryl acetic acid derivatives provided an entry into several other types of ketones. For example, the phenol ester **11g** underwent Fries rearrangement to yield the aryl, benzyl ketone **18** as a single regioisomer.[22] The thiol ester **19** was formed in good yield, and then converted into the ketone **20** under reaction conditions introduced by Liebeskind and coworkers.[23] Finally, we exploited the ability of morpholine amides to react with hard nucleophiles to provide ketones.[17] In the event, Grignard reagents proved too basic for these transformations, and enolate formation dominated the reaction. However, we found that $LaCl_3{\cdot}2LiCl$ promoted these additions effectively. This additive, introduced by Knochel and colleagues,[24] assists nucleophilic addition to acidic aldehydes,[25] but this is the first report of its use to facilitate addition to morpholine amides.[26] Thus, a primary and a secondary Grignard reagent performed well, as did a vinyl and phenyl reagent. No tertiary alcohols were observed from double addition. Taken together, these examples demonstrate that the ketene surrogate coupling provides efficient access to aryl, vinyl and alkyl ketones.

Finally, taking inspiration from the Danheiser benzannulation,[27] we developed a new benzannulation protocol as outlined in Scheme 3.[28] 2-Iodostyrenes (**22**, X = CH) were found to couple with *tert*-butoxy electrocyclic ringacetylene, rearrange to the aryl ketene, and undergo 6 electrocyclic ring closure to provide the naphthols **23a–23c** in good yield. The substituted styrenes leading to **23b** and **22c** were used as mixture of E and Z isomers, and both isomers appear to participate in the sigmatropic rearrangement. The annulation was also successful with 2-vinyl-3-iodopyridine to generate quinoline **23d**, and even showed modest success with the imine derived from 2-iodoaniline (**23e**).

In summary, we have found that *tert*-butoxy acetylene serves the role of metalated ketene in cross-coupling reactions. It can undergo Sonogashira coupling with aryl iodides, and then transform into a ketene under mild thermal conditions. This ketene surrogate coupling leads to aryl acetic acid derivatives, ketones, allenes and cyclobutanone products in good yield. An advantageous characteristic of the ketone surrogate coupling is the ability to access a wide range of carbonyl compounds from a single intermediate. Moreover, an efficient benzannulation process has been developed to provide hydroxy naphthylenes and hydroxy quinolines.

Experimental Section

Representative procedure

Aryl iodide (0.3 mmol), $Pd_2(dba)_3$ (15.6 mg, 0.015 mmol), PPh_3 (15.9 mg, 0.06 mmol), CuI (7.5 mg, 0.039 mmol), and 150 mg 4 Å molecular sieves were combined in a vial and purged with argon. Diisopropylethyl amine (0.6 mL) and *tert*-butoxyacetylene (0.6 mL) were added at room temperature. The reaction was stirred at room temperature until it reached completion (12–24 h), and was then directly loaded onto an Al_2O_3 plug and eluted with ethyl acetate and hexane (1:10). The crude ynol either was dissolved in toluene (2.0 mL), and morpholine (0.2 mL) was added. The reaction mixture was heated to 75 00B0;C for 3 h, cooled, and concentrated under reduced pressure. Pure morpholine amides were isolated following flash chromatography on silica gel.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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16. We found wide variations in the yields when different batches of $Pd(PPh_3)_4$ from SigmaAldrich were used, while those from Strem were more consistent. High reactivity could be rescued by increasing the copper loading to 20 mol%. It is possible that higher levels of PPh3 may poison the copper co-catalyst, which can be overcome with additional copper. Reactions with $Pd_2(dba)_3$ + PPh_3 were uniformly reproducible.
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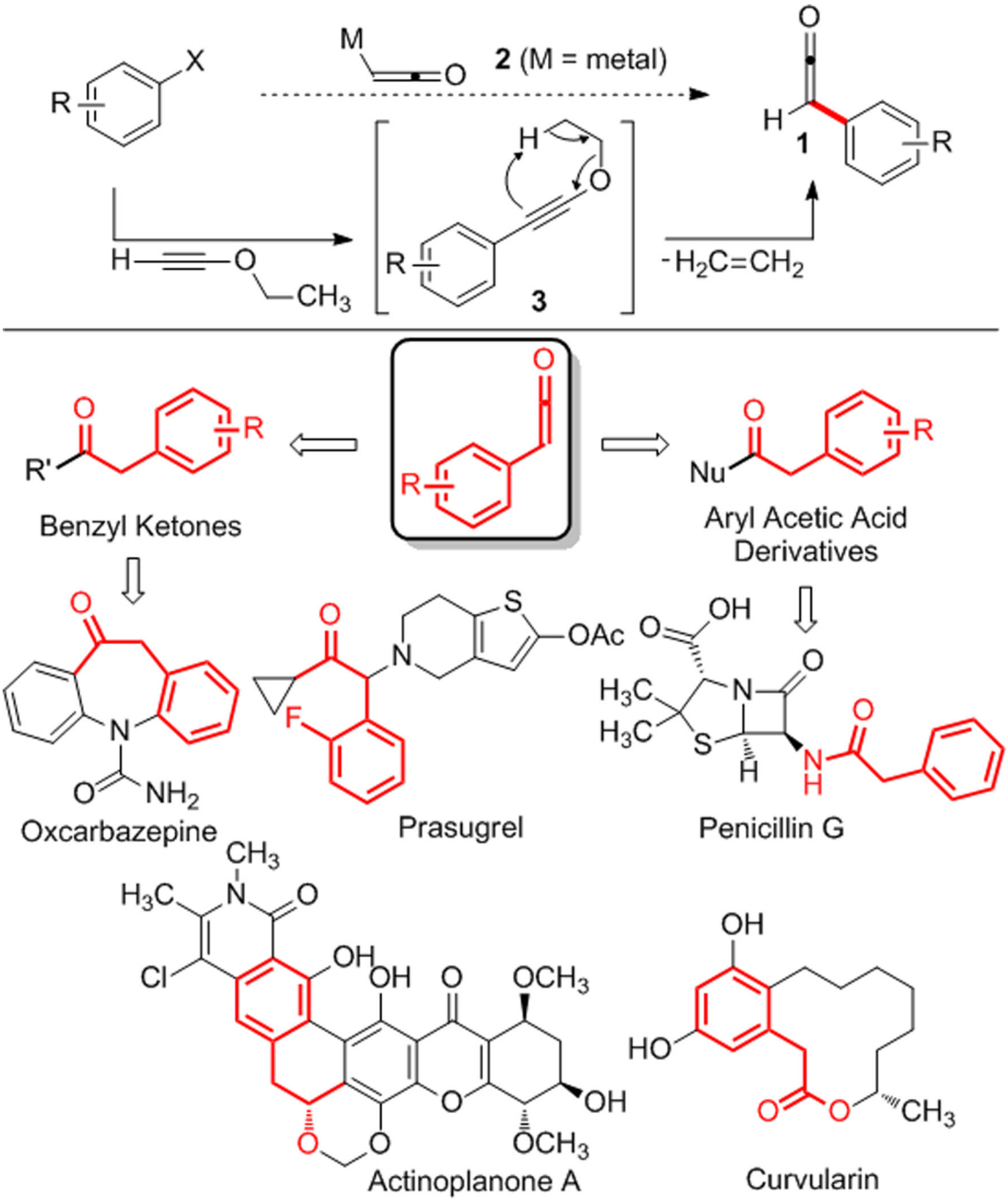
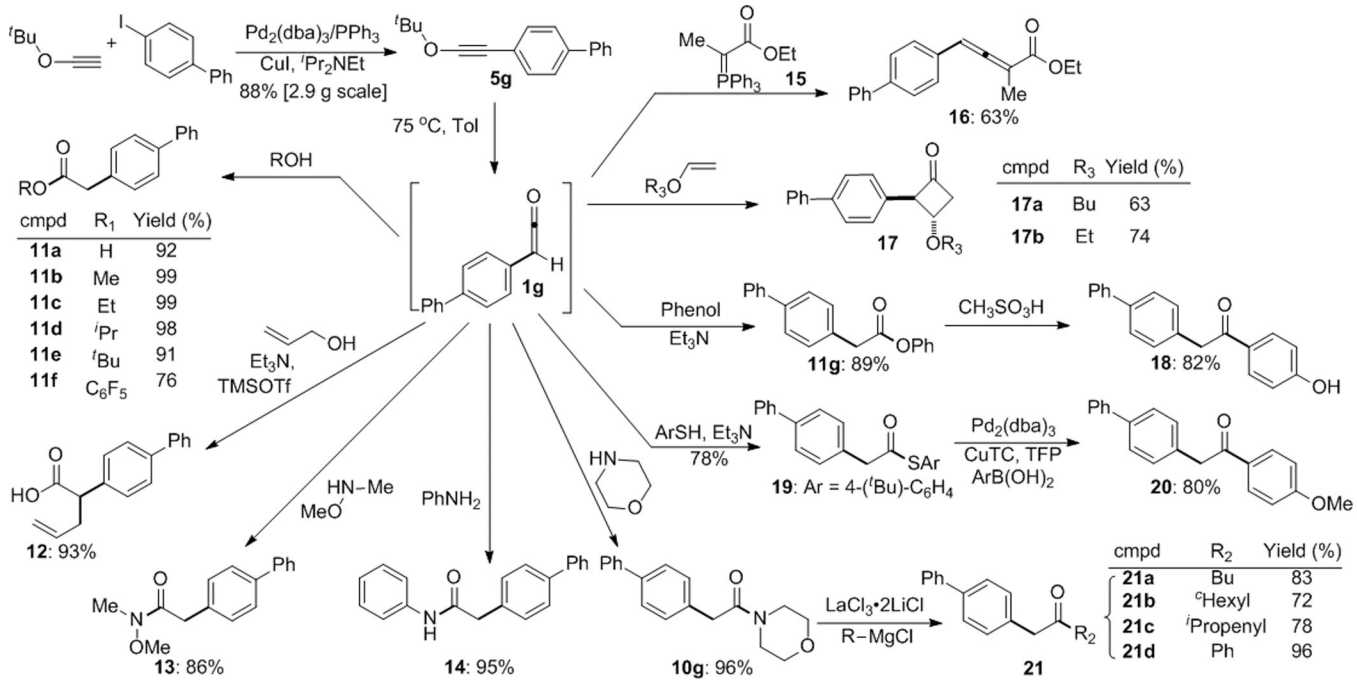


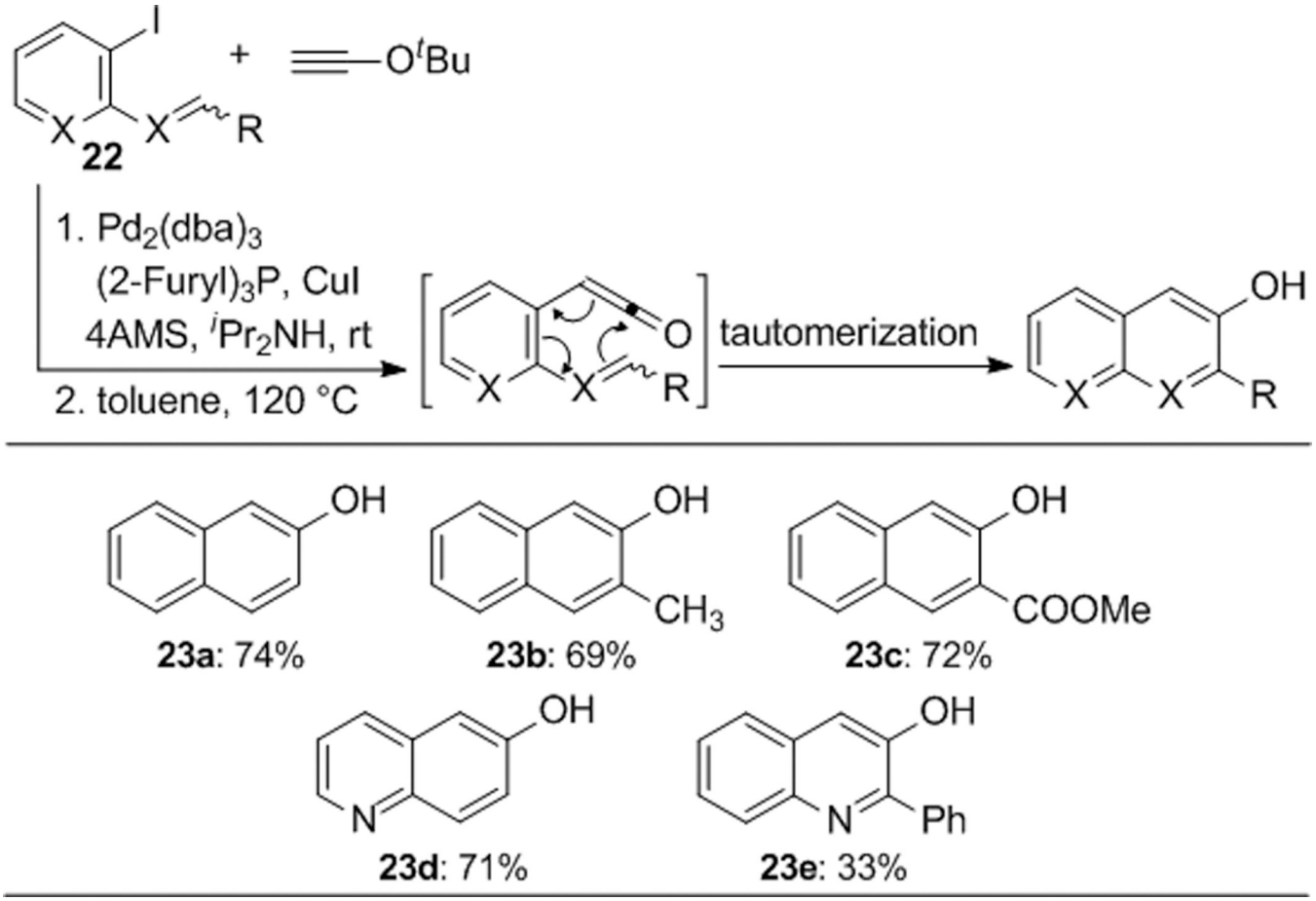
Scheme 1.

Coupling of ynol ethers with aryl halides to yield aryl ketenes.



Scheme 2.

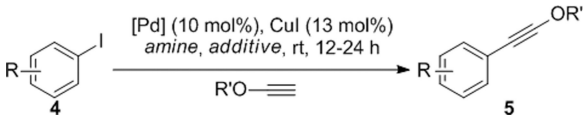
Aryl acetic acid derivatives and benzyl ketones via ketene trapping



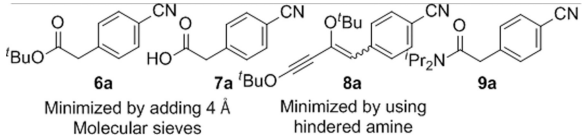
Scheme 3.
Benzannulation with *tert*-butoxyacetylene.

Table 1

Optimization of Coupling Conditions.[a]



entry	R	R'	catalyst	amine	additive	yield (%)[b]
1	4-CN (**4a**)	Et	$Pd(PPh_3)_4$	Et_3N	-	<5
2	4-CN	^{t}Bu	$Pd(PPh_3)_4$	Et_3N	-	54
3	4-CN	^{t}Bu	$Pd(PPh_3)_4$	$^i Pr_2NEt$	4Å MS	85
4	4-CN	^{t}Bu	$Pd_2(dba)_3/PPh_3$[c]	$^i Pr_2NEt$	4Å MS	95
5	4-Me (**4b**)	^{t}Bu	$Pd_2(dba)_3/PPh_3$[c]	$^i Pr_2NEt$	4Å MS	66
6	4-Me	^{t}Bu	$Pd_2(dba)_3/PPh_3$[c]	$^i Pr_2NH$	4Å MS	89
7	2-Me (**4c**)	^{t}Bu	$Pd_2(dba)_3/PPh_3$[c]	$^i Pr_2NH$	4Å MS	55
8	2-Me	^{t}Bu	$Pd_2(dba)_3$/TFP[c],[d]	$^i Pr_2NH$	4Å MS	79



Minimized by adding 4 Å Molecular sieves | Minimized by using hindered amine

[a] Reactions were conducted on a 0.1 mmol scale, 0.25 M in 1:1 (v:v) amine:ynol ether.

[b] NMR yields based on an internal standard.

[c] 20 mol% phosphine was used.

[d] TFP = tri(2-furyl)phosphine.

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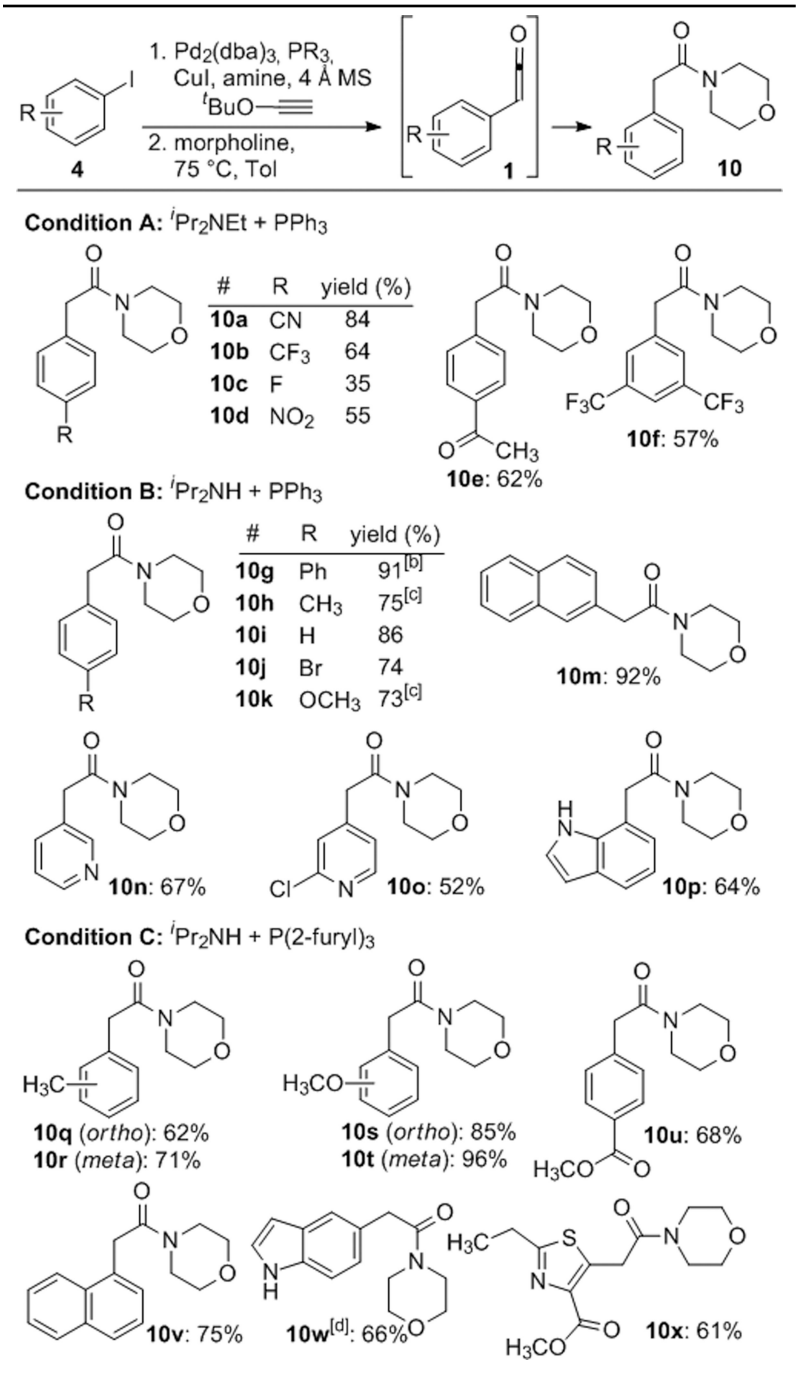
Table 2

Ketene Surrogate Coupling Scope



[a] Isolated yields over 2 steps. Reactions were conducted on a 0.3 mmol scale unless otherwise noted, 0.25 M in 1:1 (v:v) amine:ynol ether with 5 mol% $Pd_2(dba)_3$, 20 mol% phosphine, and 13 mol% of CuI for 12–24 h at rt.

[b] 3 mmol scale.

[c] 1 mmol scale.

[d] 48 h reaction time.