Ketenes Hot Paper

DOI: 10.1002/ange.201405036

The Ketene-Surrogate Coupling: Catalytic Conversion of Aryl Iodides into Aryl Ketenes through Ynol Ethers**

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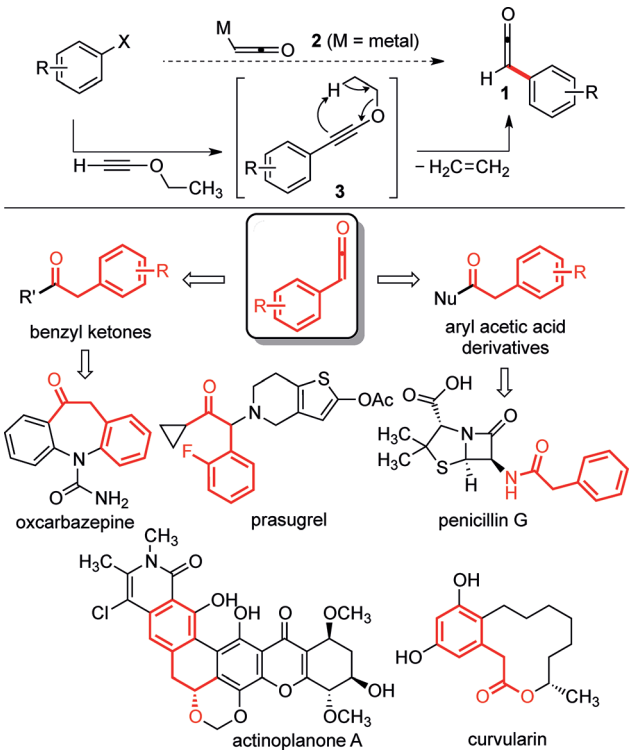
Abstract: *tert-Butoxyacetylene is shown to undergo Sonogashira coupling with aryl iodides to yield aryl-substituted tert-butyl ynol ethers. These intermediates participate in a [1,5]-hydride shift, which results in the extrusion of isobutylene and the generation of aryl ketenes. The ketenes are trapped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

Benzyl ketones and aryl acetic acid derivatives are found in many biologically active natural products and drug 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 general catalytic method to prepare these substructures. Herein we report a novel cross-coupling between aryl iodides and ynol ethers that provides access to aryl ketenes (**1**), thus providing a general catalytic synthesis of benzyl carbonyl compounds.

Previous catalytic approaches to aryl acetic acid derivatives have relied on arylation of enolates. Nickel and palladium 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 monoarylation can be challenging. Alternative catalytic approaches to the α-arylation of carbonyl compounds include α-arylation with iodonium salts[2] or activated sulfoxides,[3] addition of aldehydes to in situ generated quinone derivatives,[4] and a recent oxidative coupling of ketones with nitroarenes.[5]



Scheme 1. Coupling of ynol ethers with aryl halides to yield aryl ketenes.

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 for coupling a 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, and indicates that this transformation is reliable and occurs under mild reaction conditions.[9] In contrast, the cross-coupling of alkoxyacetylenes remains poorly developed. In

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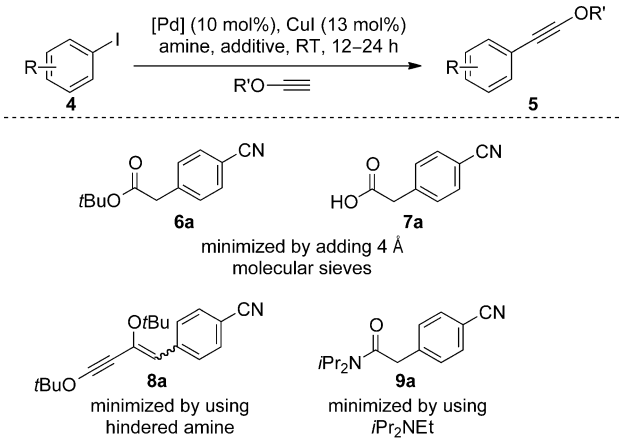
[**] Funding provided by the NIH (R01GM102403) and the Welch Foundation (I-1612). We thank Dr. Karen S. MacMillan (UT Southwestern) for preliminary experiments related to the synthesis of anilides and Jibao Xia (UT Southwestern) for independently repeating the synthesis of **10g**, and Prof. Gary Sulikowski for suggesting the Fries rearrangement to synthesize the ketone **18**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405036.

this context, Stille coupling of alkoxyethynyl tin reagents has been described,[10] but Sonogashira coupling could directly connect the aryl iodides and ynol ethers without necessitating prefunctionalization of the acetylene motif. While the Sonogashira coupling between menthol-derived ynol ethers and terminal vinyl iodides has been investigated,[11] the only Sonogashira 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 palladium-catalyzed coupling of alkyl ynol ethers with aryl iodides. 4-Cyanoiodobenzene (**4a**) was combined with ethoxy acetylene, $[Pd(PPh_3)_4]$, and CuI in triethyl amine (Table 1, 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*-butoxyacetylene.[14] In addition to being more stable, *tert*-butoxyacetylenes rearrange to ketenes at around 80°C compared to 120°C, which is required for conversion of ethoxyacetylenes into ketenes.[15] We were encouraged by the formation of the alkyne **5a** in 54% yield when *tert*-butoxyacetylene was used (entry 2). The reaction also generated products arising from hydration and hydrolysis of **5a** (**6a** and 7**a**, respectively), and the enyne **8a**, an adduct arising from *tert*-butoxyacetylene and the aryl iodide reacting in a 2:1 ratio.

Table 1: Optimization of coupling conditions.[a]



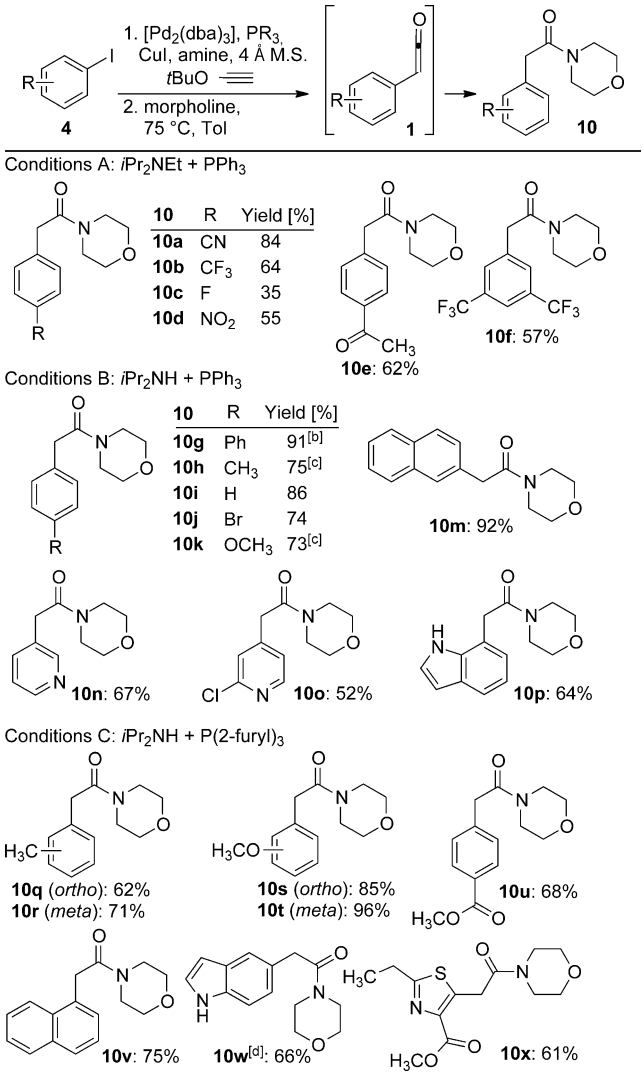
Entry	R^1	R^2	Catalyst	Amine	Additive	Yield [%][b]
1	4-CN (**4a**)	Et	$[Pd(PPh_3)_4]$	Et_3N	–	< 5
2	4-CN	*t*Bu	$[Pd(PPh_3)_4]$	Et_3N	–	54
3	4-CN	*t*Bu	$[Pd(PPh_3)_4]$	iPr_2NEt	4 Å M.S.	85
4	4-CN	*t*Bu	$[Pd_2(dba)_3]/PPh_3$[c]	iPr_2NEt	4 Å M.S.	95
5	4-Me (**4b**)	*t*Bu	$[Pd_2(dba)_3]/PPh_3$[c]	iPr_2NEt	4 Å M.S.	66
6	4-Me	*t*Bu	$[Pd_2(dba)_3]/PPh_3$[c]	iPr_2NH	4 Å M.S.	89
7	2-Me (**4c**)	*t*Bu	$[Pd_2(dba)_3]/PPh_3$[c]	iPr_2NH	4 Å M.S.	55
8	2-Me	*t*Bu	$[Pd_2(dba)_3]$/TFP[c]	iPr_2NH	4 Å M.S.	79

[a] Reactions were conducted on a 0.1 mmol scale; 0.25 M in 1:1 (v/v) amine/ynol ether. [b] Yields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Used 20 mol% phosphine. dba = dibenzylideneacetone, M.S. = molecular sieves, TFP = tri(2-furyl)phosphine.

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, iPr_2NEt, suppressed the generation of the enynol ether **8a** (Table 1, entry 3). Under these reaction conditions, the aryl-substituted ynol ether **5a** was formed in an improved 85% yield. The enynol **8a** could arise from either dimerization of *tert*-butoxyacetylene and subsequent coupling with the aryl iodide or carbometalation of the Sonogashira product **5a**. We favor the former hypothesis because *tert*-buytoxyacetylene did not add to the 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 reaction 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 reaction conditions, the 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 electron-neutral substrates. Finally, sterically hindered substrates such as **4c** benefited from an even more active catalyst. In particular, tri(2-furyl)phosphine formed a competent catalyst in conjunction with $[Pd_2(dba)_3]$, thus 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 (see Table 2). In these experiments, copper, palladium, and amines were removed by rapid chromatography using neutral Al_2O_3. In general, electron-neutral or electron-rich Sonogashira products were isolated in high purity whereas electron-poor congeners were prone to hydrolysis. For example, the ynol derived from 4-methoxyiodobenzene was stored for more than one year at 4°C with no signs of decomposition. In contrast, the *p*-CN-substituted ynol **5a** underwent hydrolysis (5–10%) upon attempted purification. Therefore, after 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. They behave similarly to Weinreb amides, but are

Table 2: Scope of ketene-surrogate coupling.



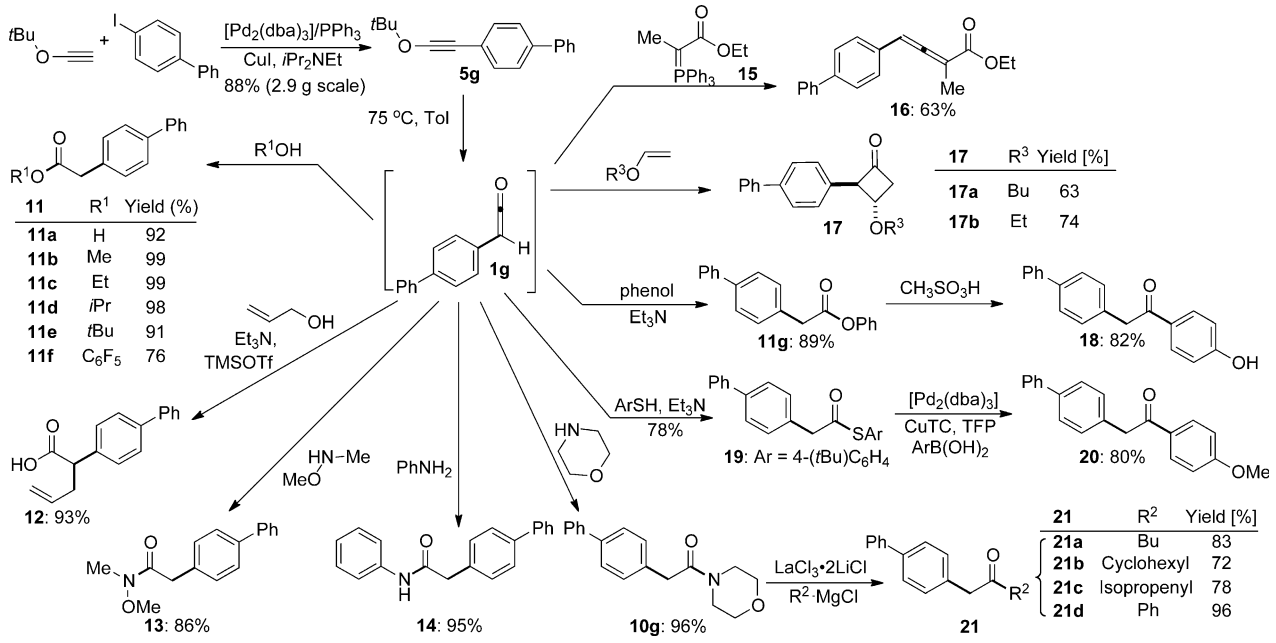
[a] Yields of products isolated after two steps. Reactions were conducted on a 0.3 mmol scale unless otherwise noted; 0.25 M in 1:1 (v/v) amine/ynol ether with 5 mol% $[Pd_2(dba)_3]$, 20 mol% phosphine, and 13 mol% of CuI for 12–24 h at RT. [b] 3 mmol scale. [c] 1 mmol scale. [d] 48 h reaction time.

more stable and less expensive.[18] We found that ketones, esters, 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**,**r**,**h**) and 2-, 3-, and 4-methoxy (**10s**,**t**,**k**) moieties, provided the corresponding morpholine amides in good yield. Both 1- and 2-iodonaphthalene were excellent substrates (**10v**,**m**). Moreover, several heterocycles participated in the reaction, yielding 3- and 4-substituted pyridines (**10n,o**) and 5- and 7-substitued indoles (**10p**,**w**). In the latter cases, the indole NH did not require protection. The thiazole **10x** was formed in good yield, thus extending the chemistry to five-membered heterocycles. Aryl bromides do not couple efficiently, but this characteristic allows selective coupling of 4-bromoiodobenzene to form the 4-bromophenyl acetamide **10j** in 74% yield. Additionally 4-fluoroiodobenzene provided **10c** in poor yield because of the volatility of the ynol ether and instability of the amide.

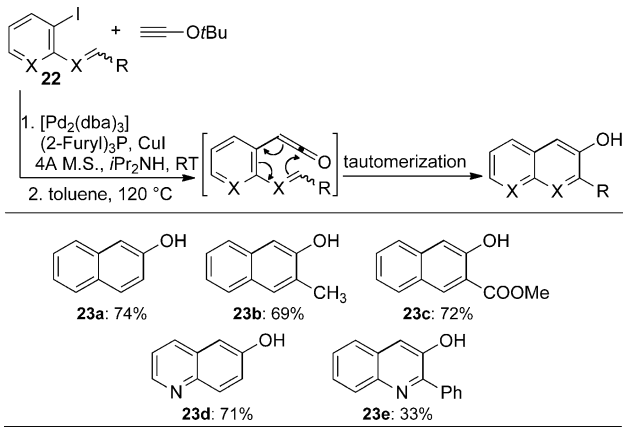
The examples in Table 2 involve trapping the arylketene with morpholine, but we wanted to explore the reactivity of this intermediate more broadly. To this end, the ynol ether **5g** was synthesized on a 2.9 g scale and isolated in 88% yield (Scheme 2). The ketene **1g** was then generated at 75 °C in 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–e** in high yield. Likewise, pentafluorophenol and phenol formed the phenolic esters **11f** and **11g**, respectively. The former could serve as a useful acylating agent while the latter can participate in a Fries rearrangement. 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 the C-allyl ester **12**.[19] In related transformations, amines other than morpholine react with equal facility. Thus, the Weinreb amide **13** emerges from trapping with (MeO)MeNH, most conveniently free-based in situ from the hydrochloride salt, and aniline reacted to form the 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, the 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 the 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 with subsequent 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 co-workers.[23] Additionally, 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 $LaCl_3{\cdot}2\,LiCl$ 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] 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



Scheme 2. Aryl acetic acid derivatives and benzyl ketones by ketene trapping. TC = 2-thiophene carboxylate, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 3. Benzannulation with *tert*-butoxyacetylene.

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*-butoxyacetylene, rearrange to the aryl ketene, and undergo 6π electrocyclic ring closure to provide the naphthols **23a–c** in good yield. The β-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 the quinoline **23d**, and even showed modest success with the imine derived from 2-iodoaniline (**23e**).

In summary, we have found that *tert*-butoxyacetylene 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 completion as determined by TLC (12–24 h), and was then directly loaded onto an Al_2O_3 plug and eluted with ethyl acetate and hexanes (1:10). The crude reaction mixture was dissolved in toluene (2.0 mL), and morpholine (0.2 mL) was added. The reaction mixture was heated to 75 °C for 3 h, cooled, and concentrated under reduced pressure. Pure morpholine amides were isolated after flash chromatography on silica gel.

Received: May 6, 2014
Published online: June 27, 2014

Keywords: arenes · cross-coupling · ketenes · palladium · synthetic methods

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