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Hauser–Heck: Efficient Synthesis of γ-Aryl-β-ketoesters en Route to Substituted Naphthalenes

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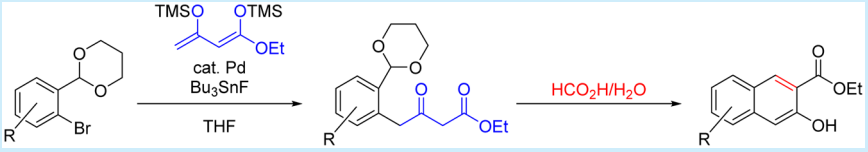
Supporting Information

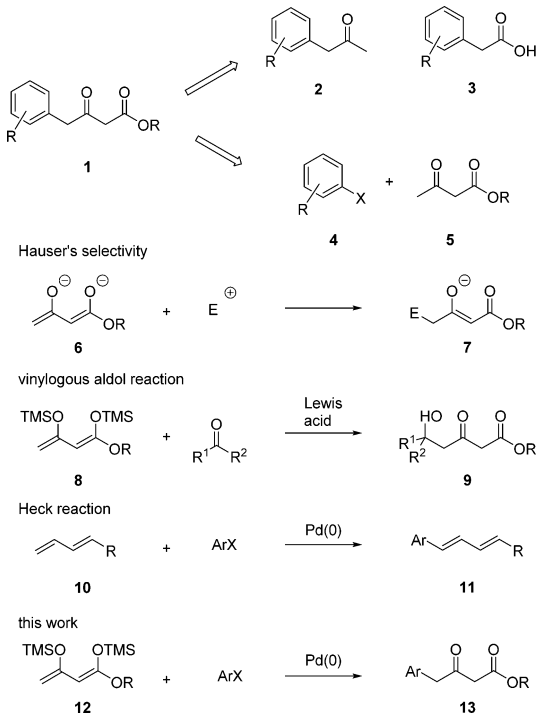


ABSTRACT: γ-Aryl-β-ketoesters can be prepared in one step from aryl bromides and bis(trimethylsilyl) enol ethers using catalytic amounts of $Pd(dba)_2$/*t*-Bu_3P and stoichiometric amounts of Bu_3SnF. The wide range of γ-(hetero)aryl-β-ketoesters that can be obtained illustrate the scope and limitations of this novel Hauser–Heck combination. γ-Aryl-β-ketoesters with a 1,3-dioxane acetal in the *ortho* position can easily be transformed into the hydroxy naphthoate in very good yield. Aqueous formic acid at 65 °C provides optimal conditions for this deprotective aromatization.

γ-Aryl-β-ketoesters of type **1** are valuable intermediates for the synthesis of complex target molecules.[1] So far, they have been synthesized from phenylacetone **2** or phenyl acetic acid **3** precursors.[2] A one-step approach using an aryl halide **4** and a β-ketoester **5** could make use of the large number of aryl halides commercially available and could provide an efficient alternative to access compounds of type **1**. Here, we disclose a general solution to this challenge.[3] The substitution of β-ketoester in the γ-position can be achieved via reaction of the dienolate **6** with appropriate electrophiles (**6** → **7**). The observed γ-regioselectivity follows Hauser's rule (Scheme 1).[4] If carbonyl compounds are used as electrophiles and bis(trimethylsilyl) enol ethers **8** as substrates, the products of a vinylogous aldol reaction (**8** → **9**) can be obtained.[5] For 1,3 dienes (**10**) a Heck reaction with aryl halides results in the formation of γ-arylated dienes (**11**).[6] The transition-metal catalyzed cross-coupling reaction of enolates with aryl halides (enolate arylation) is an established reaction but carries with it the disadvantage of high enolate basicity,[7] which can be avoided by using silyl enol ethers as enolate equivalents. Following the pioneering work of Kuwajima on the Pd-mediated regioselective arylation of silyl enol ethers,[8] optimized conditions that use metal fluoride additives have been reported.[9] Following a careful consideration of the methodology known for Hauser's selectivity, enolate-equivalent arylation, and Heck reaction, we considered it worthwhile to examine the Pd-mediated γ-arylation of bis(trimethylsilyl) enol ethers (**12** → **13**). This process might be denoted as a Hauser–Heck-type reaction. Here, we disclose the Pd-catalyzed coupling of various (hetero)aryl halides with bis(trimethyl)silyl enol ethers in the γ-position and its application in the synthesis of substituted naphthalenes.

The reaction of bromobenzene **14** with the bis(trimethylsilyl) enol ether **15**[10] to obtain the γ-phenyl-β-ketoester **16** was chosen as a test reaction for our optimization studies (Table 1). Among three Pd-catalysts screened, Pd-

Scheme 1. Regioselective γ-Substitution of β-Keto-esters



$(dba)_2$/*t*-Bu_3P gave the desired product in good yield (entry 1). The use of RuPhos Pd-G2 also resulted in good yields, but only for selected substrates, it lacking in overall generality (entry 3). With regard to reaction temperature, a minimum of 65 °C was optimal for a satisfying yield (entries 1, 4, 5, 6). As described for

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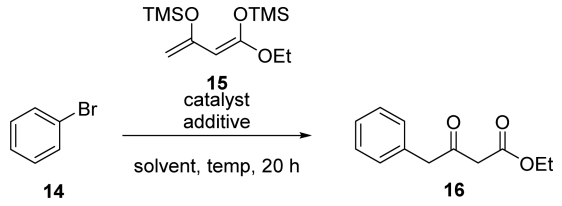
Table 1. Optimization of Reaction Conditions



entry	cat.	additive	solvent	temp (°C)	yield (%)[a]
1	A	Bu_3SnF (1.4 equiv)	toluene	85	69
2	B	Bu_3SnF (1.4 equiv)	toluene	85	65
3	C	Bu_3SnF (1.4 equiv)	toluene	85	70
4	A	Bu_3SnF (1.4 equiv)	toluene	65	73
5	A	Bu_3SnF (1.4 equiv)	toluene	45	5
6	A	Bu_3SnF (1.4 equiv)	toluene	25	0
7	A	Bu_3SnF (1.2 equiv)	toluene	65	46
8	A	Bu_3SnF (1.4 equiv)	THF	65	76
9	A	ZnF_2 (0.5 equiv)	DMF	80	69
10	A	Bu_3SnF (1.4 equiv) CsF (1.4 equiv)	toluene	65	0

[a]Isolated yields. Catalyst A: $Pd(dba)_2$ (5 mol %)/*t*-Bu_3P (6 mol %). Catalyst B: $Pd(OAc)_2$ (5 mol %)/*t*-Bu_3P (9 mol %). Catalyst C: RuPhos Pd-G2 (5 mol %).

simple enol ethers,[8,9] Bu_3SnF as a stoichiometric additive was important in all cases but no synergistic effect[9a] of two metal fluorides was observed (entry 10). Besides toluene, THF was found to be a suitable solvent (entry 8). In DMF as solvent, ZnF_2 could be used as an additive (entry 9).[9c]

The optimized reaction conditions were utilized to perform the reaction with a variety of different (hetero)aryl halides **14** and two bis(trimethylsilyl) enol ethers **15** and **18**; they yielded the γ-aryl-β-ketoesters **16** and **17** with the results summarized in Figure 1. The arylation products were formed in moderate to very good yields. Steric encumbrance in the case of the electron-rich 2-bromotoluene turned out to be of no significance (**16c**, **17c**). A highly electron-donating amine lowered the yields as expected (**16d**, **17d**), whereas the electron-withdrawing nitro group (**16e**, **17e**) was tolerated just like an ester, (**16f**, **17f**) which remained untouched if exposed to the reaction conditions. With respect to heteroaromatic compounds, 2-bromothiophene (**16h**, **17h**) as well as the nitrogen-containing compounds 3-bromopyridine and 3-bromoquinoline (**16g**, **16i**, **17g**, **17i**) were determined to be suitable reaction partners. As shown in the optimization studies, the reaction can be carried out using toluene as a solvent, which has proven to be superior in some cases. With respect to aryl chlorides, the yields obtained were around 10%. The use of 1-bromo-4-iodobenzene resulted in a complex mixture of products.

Our motivation for an efficient synthetic access to γ-aryl-β-ketoester arose from a material-science-directed project dealing with the synthesis of oligo(pent)acenes.[11a] Key intermediates for the synthesis of these target molecules are 3-hydroxy-naphthyl-2-carboxylates[11b] of type **19** (Scheme 2). Retrosynthetically, naphthalene **19** could be obtained by an intramolecular aldol condensation from the β-ketoester aldehyde **20** where the latter would be accessible from the γ-arylation of the bis(trimethylsilyl) enol ether **12** with the aryl bromide **21**. Because of the incompatibility of an aldehyde with the optimized Hauser–Heck conditions, an aldehyde equivalent had to be used instead.

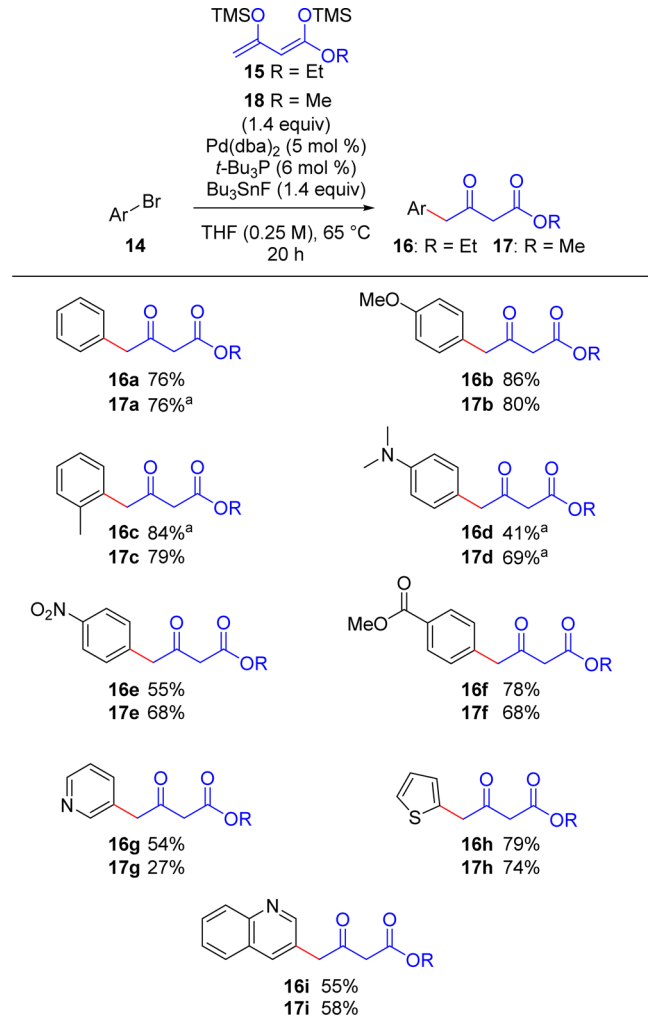
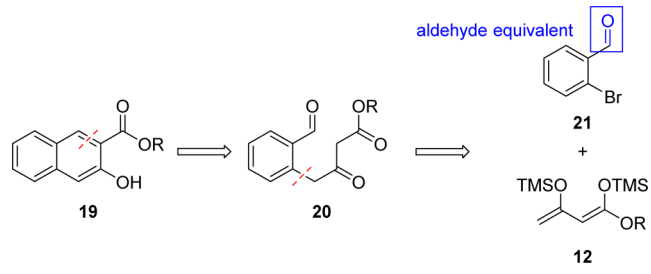


Figure 1. Scope and limitations. Reactions were conducted with 1 equiv of aryl halide and 1.4 equiv of bis(trimethylsilyl) enol ether. [a] Toluene was used. All yields are isolated yields.

Scheme 2. Retrosynthetic Approach to Substituted Naphthalenes



A first attempt for an aldehyde equivalent focused on a protected alcohol for the Pd-mediated γ-arylation of the bis(trimethylsilyl) enol ether (Scheme 3). The starting point was the aryl bromide **22**.[12] The γ-arylation with the bis(trimethylsilyl) enol ether **23** gave the β-ketoester **24** in good yield. Deprotection of the THP ether resulted in formation of the hemiacetal **25**, which was in equilibrium with its hydroxyketone. Therefore, we submitted this equilibrium mixture to a Dess-Martin oxidation resulting in the formation of the desired naphthalene **27** in a mere 8% yield,

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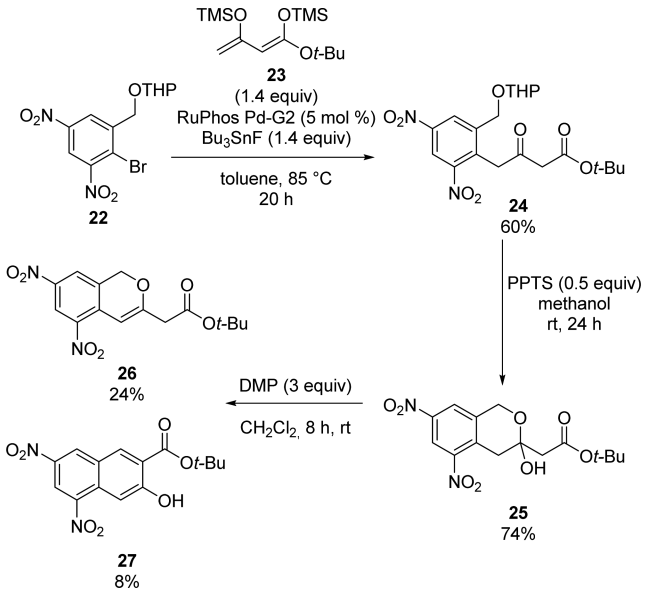
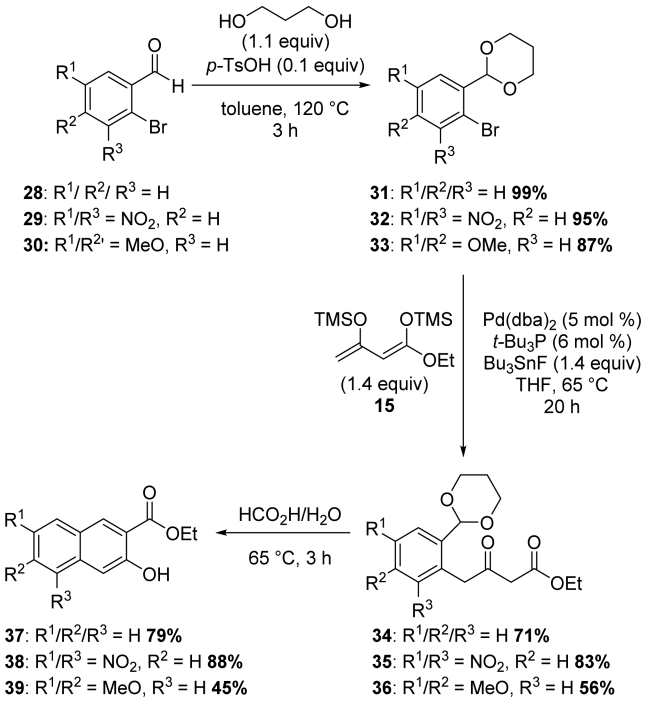
Scheme 3. First Attempts in the Synthesis of Naphthalene 27 Starting from the Protected Alcohol 22



with dehydration of **25** to the isochromene **26** being the major product.

Based on the previous results, we considered it advantageous to use an aryl bromide for the γ-arylation where the oxidation state of the aldehyde was already set. We therefore chose an acetal as an aldehyde equivalent, which was subjected to our optimized reaction conditions. We expected the resulting diketo-acetal to undergo cyclization and aromatization when exposed to aqueous acidic media. Toward this end, three different bromo aldehydes **28**, **29**, and **30** were converted into the corresponding acetals **31**, **32**, and **33** (Scheme 4). The γ-arylation with the bis(trimethylsilyl) enol ether **15** using the

Scheme 4. Access to Substituted Naphthalenes



optimized conditions gave β-ketoesters **34** and **35** in very good yield. For the case of the electron-rich dimethoxy substrate **33**, a satisfactory 58% yield of the arylation product **36** was obtained. The final deprotective aromatization of the β-ketoester acetal to the hydroxy naphthoate under acidic conditions needed extensive optimization (vide infra). Aqueous formic acid at 65 °C was identified as the optimal set of conditions for this step. For hydroxy naphthoates **37** and **38** very good yields were achieved (79 and 88%), while for the dimethoxy naphthol **39**, a lower yield (45%) was obtained. The structure of the substituted naphthalenes was proven by X-ray crystal structures for **38** and **39** (Figure 2) as well as for **27** (see

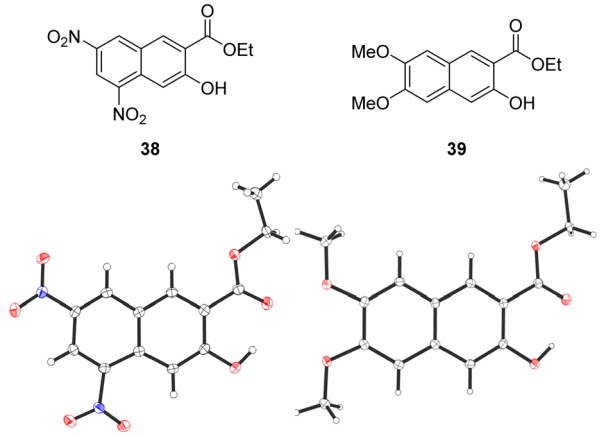
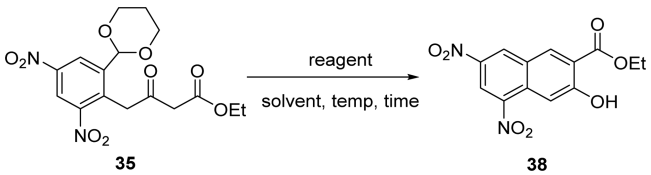


Figure 2. X-ray structures of naphthalenes **38** and **39**.

Supporting Information). The successful deprotective aromatization of the β-ketoester acetal moiety to the hydroxy naphthoate was the result of an intensive optimization study which is summarized for **35** → **38** in Table 2. A 1,3-dioxane was chosen as the acetal because it could be hydrolyzed more easily than a 5,5-dimethyl-1,3-dioxane or a dioxolane.[13]

Aqueous acetic acid at elevated temperatures is a typical reagent for the deprotection of 1,3-dioxanes.[14] Reaction temperatures between 75 and 100 °C gave the desired deprotection and intramolecular aldol condensation (**35** →

Table 2. Test Reactions for the Ring Closing Reaction[a]



entry	reagent	solvent	time (h)	temp (°C)	yield (%)[b]
1	AcOH/piperidine	benzene	24	80	decomp.
2	80% AcOH	H_2O	24	100	27
3	80% AcOH	H_2O	24	90	45
4	80% AcOH	H_2O	24	75	32
5	*p*-TsOH (cat.)	toluene/ H_2O	6	120	no reaction
6	37% HCl (5 equiv)	THF	3	45	decomp.
7	TFA	THF	6	45	decomp.
8	80% HCO_2H	H_2O	3	65	88

[a]Test reactions were run in 50 mg scale. [b]Yield of isolated product.

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38) albeit in low yields (entries 2, 3, 4). Attempts to use stronger acids gave mixed results: *p*-TsOH in toluene/H_2O failed, probably due to solubility problems (entry 5). Strong acids such as HCl or TFA led to decomposition (entries 6, 7). Finally, 80% aqueous formic acid which is 1 pK_A stronger than acetic acid, at 65 °C was found optimal to produce the desired naphthoate in 88% yield (entry 8). Knoevenagel-type conditions (entry 1) gave decomposition of starting material.

In summary, we have developed an efficient one-step synthesis of γ-aryl-β-ketoesters from aryl bromides and bis(trimethylsilyl) enol ethers. Catalytic amounts of Pd-$(dba)_2$/P*t*-Bu_3 and stoichiometric amounts of Bu_3SnF were optimal conditions for this novel Hauser−Heck combination. Scope and limitations of the new method have been described for a series of aromatic and heteroaromatic examples. γ-Aryl-β-ketoesters with a 1,3-dioxane acetal in the *ortho* position can be converted efficiently into substituted naphthalenes using aqueous formic acid at 65 °C. This straightforward synthesis yields substituted naphthalenes as promising building blocks for the synthesis of oligoacenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02952.

Crystallographic data for **27**, **38**, and **39** (CIF)
Experimental details; spectroscopic and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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