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Pd(II)-Catalyzed Olefination of Electron-Deficient Arenes Using 2,6-Dialkylpyridine Ligands

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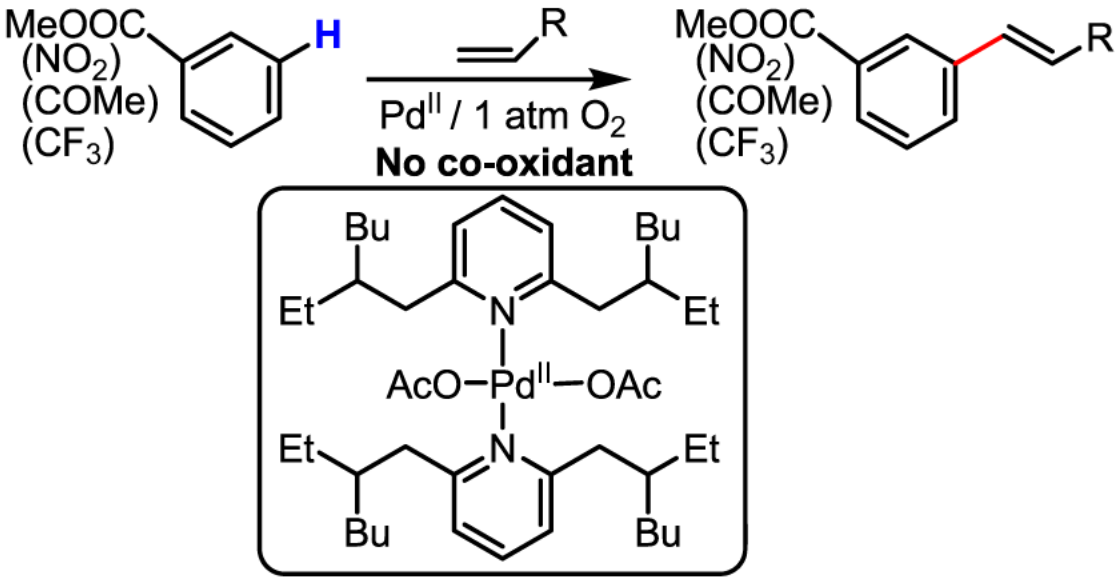
Abstract



Pd(II)-catalyzed *meta*-olefination of highly electron deficient arenes is achieved through the use of a rationally designed mutually repulsive ligand. The combination of directed and non-directed C–H functionalization of arenes provides a versatile route for the synthesis of highly sought-after 1,2,4-trisubstituted arenes.

Since the discovery of the Pd-catalyzed olefination of benzene by Fujiwara, substantial progress has been made to improve the efficiency and practicality of this reaction.[1] To date, reactivity is still limited to electron rich arenes,[1-4] except for a single example using chlorobenzene, a moderately electron deficient arene.[1c] Furthermore, olefination of *mono*-substituted arenes gives an approximately even mixture of *ortho*-, *meta*- and *para*-olefinated products,[1c] limiting possible synthetic applications. The *ortho*-olefination of benzoic acids and anilides via directed C–H activation reported by Miura and de Vries, respectively, represents an important approach to control the regioselectivity of this reaction.[5,6] Herein, we report the first example of a *meta*-selective olefination process of highly electron deficient arenes. This reaction is promoted by a novel mutually repulsive 2,6-dialkylpyridine ligand,

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Supporting Information Available: Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

allowing for the use of 1 atm O_2 as the stoichiometric oxidant in the absence of a co-oxidant. Combining this newly observed *meta*-C–H olefination with a subsequent directed *ortho*-C–H arylation provides a novel synthetic route to 1,2,4-trisubstituted arenes, a highly useful but synthetically challenging class of compounds in medicinal chemistry.[7]

Our efforts began by exploring possible conditions for Pd(II)-catalyzed C–H olefination of 1,3-bis(trifluoromethyl)benzene, a highly electron deficient and unreactive substrate. Pioneering work on C–H activation and subsequent homocoupling of α,α,α-trifluorotoluene has been reported by Bercaw using a cationic complex [(α-diimine)Pd(CH_3)(H_2O)][BF_4].[8] Beyond its highly electron-deficient character, the use of 1,3-bis(trifluoromethyl)benzene[9] also allowed us to avoid complications associated with the formation of multiple regioisomers during our screening process. Initial investigations into Fujiwara-type reactions using electron-deficient arenes under various reported conditions[1] revealed two major problems (Table 1, entry 1). First, electron deficient arenes were unreactive due to their poor coordination with a $Pd(OAc)_2$ catalyst. Second, reoxidation of Pd(0) by O_2 was not possible in the absence of electron rich arenes, external ligands or co-oxidants.

Since pyridyl groups (Py) are among the most efficient ligands to promote the reoxidation of Pd(0) by oxygen,[10] we first tested pyridine and 2, 6-lutidine, two common pyridine-based ligands (Table 1, entries 2 and 3), both of which demonstrated low reactivity. We hypothesized that in these systems, displacement of the pyridyl ligand by the electron-deficient arene substrate is energetically disfavored due to the strength of the Pd–N bond. Even upon prior loss of acetate and formation of the corresponding $Py_2Pd(OAc)^+$ species, the resulting complex remained insufficiently electrophilic for C–H activation to take place.[11] This observation led us to examine pyridyl ligands that would exhibit weaker Pd–N bond strength. We envisioned that an increase in steric bulk at the 2 and 6 positions of the pyridine ring would accomplish this goal, but these ligands were also ineffective (entries 4 and 5), presumably because their binding strength to Pd(II) or Pd(0) was relatively weak, as evidenced by a high level of Pd(0) precipitation formed from the predominant Wacker oxidation pathway. Lastly, we hypothesized that the introduction of an electron-withdrawing group in the pyridine ring would similarly weaken the Pd–N bond, but unfortunately, the previously used ethyl nicotinate ligand was ineffective (entry 6).[2b]

These findings prompted us to design a novel ligand that would coordinate with Pd(II) effectively, but in a singly bound fashion to allow for substrate binding. We envisioned that this goal could be achieved using 2, 6-disubstituted pyridines with minimal steric hindrance immediately surrounding the nitrogen atom and with steric hindrance instead placed on the side chain carbon atoms. In gradually increasing the steric bulk on these remote carbon atoms, we hypothesized that a given pair of ligands would sense significant mutual steric repulsion when both were coordinated to the Pd(II) center. As a consequence, only one ligand would coordinate to Pd(II), allowing for substrate binding to take place. Following this rationale, a series of ligands with varying steric hindrance along the side chains was prepared. We were pleased to find that ligands **L1**–**L3** indeed promoted the olefination of the electron-deficient substrate **1** to give the *meta*-olefinated product in 20-50% yield by ^{1}H NMR (Table 1, entries 7 to 9). Ligand **L3** with the longest and most branched side chain displayed better reactivity (entry 9). Monitoring the reaction by ^{1}H NMR showed that the ligand remained intact throughout the reaction course.

We also found that the use of 1 equiv of Ac_2O as an additive increased the reaction yields by 10-20%. Although the role of Ac_2O as a drying agent for the Fujiwara reaction has been proposed,[1b] substituting molecular sieves for Ac_2O in our reaction was not effective. It is possible that after the insertion of O_2 into the Pd–H species, AcO–Pd–OOH[10a] reacts with Ac_2O to generate $Pd(OAc)_2$ thereby accelerating the turnover.

To test the generality of the observed *meta*-regioselectivity, broadly useful electron deficient arenes **1**–**7** were also reacted with either acrylate or cinnamate substrates under the same conditions (Table 2). In most cases, *meta*-selectivity was observed. With cinnamate, a mixture of *E*/*Z*-isomers was obtained, with the *E*-isomer as the major product; this selectivity is similar to that observed in the Heck coupling reactions (entry 1).[12] Notably, olefination of **1**–**7** with ethyl acrylate in the absence of ligand **L3** under otherwise identical conditions gave the desired products in less than 15% yield. Hydrogenation of the olefinated products from **2–4** was performed using H_2/Pd/C when the separation of *E*- and *Z*-isomers was difficult (entries 5-7). Under these conditions, the acetyl group was reduced to an ethyl group (entry 6) and the nitro group to an amino group (entry 7). Olefination with other olefins gave similar results (entries 9 to 11). Benzene is also a suitable substrate (entry 14). The use of 5 mol% $Pd(OAc)_2$ gave lower yield (entry 4).

The use of arene substrates as neat solvent is a known drawback of the Fujiwara reaction considering that many aryl synthetic intermediates are solids. We therefore tested the feasibility of performing this reaction in commonly used solvents (see SI). We found that a minimum of 5 equiv of arene substrate **2** in ethyl acetate is required to give the olefinated product in synthetically useful yield (Table 2, entry 3).

To demonstrate the utility of this unprecedented regioselective C–H functionalization, we used a synthetically useful benzoate as the starting material to access 1, 2, 4- and 1, 2, 4, 5-substituted arenes via a sequence of non-directed and directed C–H activation (Scheme 2). *para*-Substitution in substrate **10** allowed for exclusive *meta*-functionalization. Intermediates **11** and **12** were iodinated[13] or arylated[14] to give different products, thus demonstrating versatility of this method. This synthetic route can be applied to a wide range of substrates, as C–H activation directed by carbonyl[15] and nitro groups[16] in **3** and **4** has also been established previously. Notably, 1, 2, 4-substituted arenes are the most sought after and difficult to make arene precursors in the pharmaceutical industry.[7]

While the detailed origin of the effectiveness of ligand **L3** remains to be elucidated, we have obtained preliminary experimental data in support of our rationale for the ligand design. We prepared complex *trans*-**L3**$_2$Pd(OAc)$_2$ (**C1**) by stirring 1 equiv of $Pd(OAc)_2$ with 2 equiv ligand **L3** in hexanes, a non-coordinating solvent. The structure of **C1** was then characterized by X-ray crystallography. Although this complex has a similar structure to other $Py_2Pd(OAc)_2$ complexes,[17] the bond length of Pd–N is 0.05 Å longer than that of $(Pyridine)_2Pd(OAc)_2$. Importantly, ^{1}H NMR showed that one ligand **L3** dissociates from **C1** in solution to form a new complex (Fig. 1). Notably, other $Py_2Pd(OAc)_2$ complexes are highly stable under the same conditions. While the newly formed complex has not been fully characterized, its ^{1}H NMR data is consistent with a dimeric complex **C3** (the ratio of the OAc and ligand is 4:2, see SI) rather than a trimeric analogue of which similar structures have been previously identified.[18] The formation of complex **C3** is potentially responsible for the observed reactivity.

Although the loss of reactivity at the *ortho*-C–H bond could be attributed to a steric influence from the ligand, the exact origin of the *meta*-selectivity over *para*-selectivity remains unclear. An electrophlilic substitution ($S_{Ar}E$) at the *meta*-position appears to be a plausible explanation, although the stronger acidity of the *meta*-C–H bond could also exert an influence on the regioselectivity if a proton abstraction by acetate is involved.[11, 19]

In summary, we have developed a mutually repulsive ligand **L3** that coordinates strongly, yet in a singly bound fashion, to $Pd(OAc)_2$. Complex **L3**$_2$Pd(OAc)$_2$ is a reactive pre-catalyst that catalyzes *meta*-selective C–H activation of electron deficient arenes. A non-directed and directed C–H activation sequence demonstrates the potential power of this reaction in the synthesis of 1, 2, 4-trisubstituted arenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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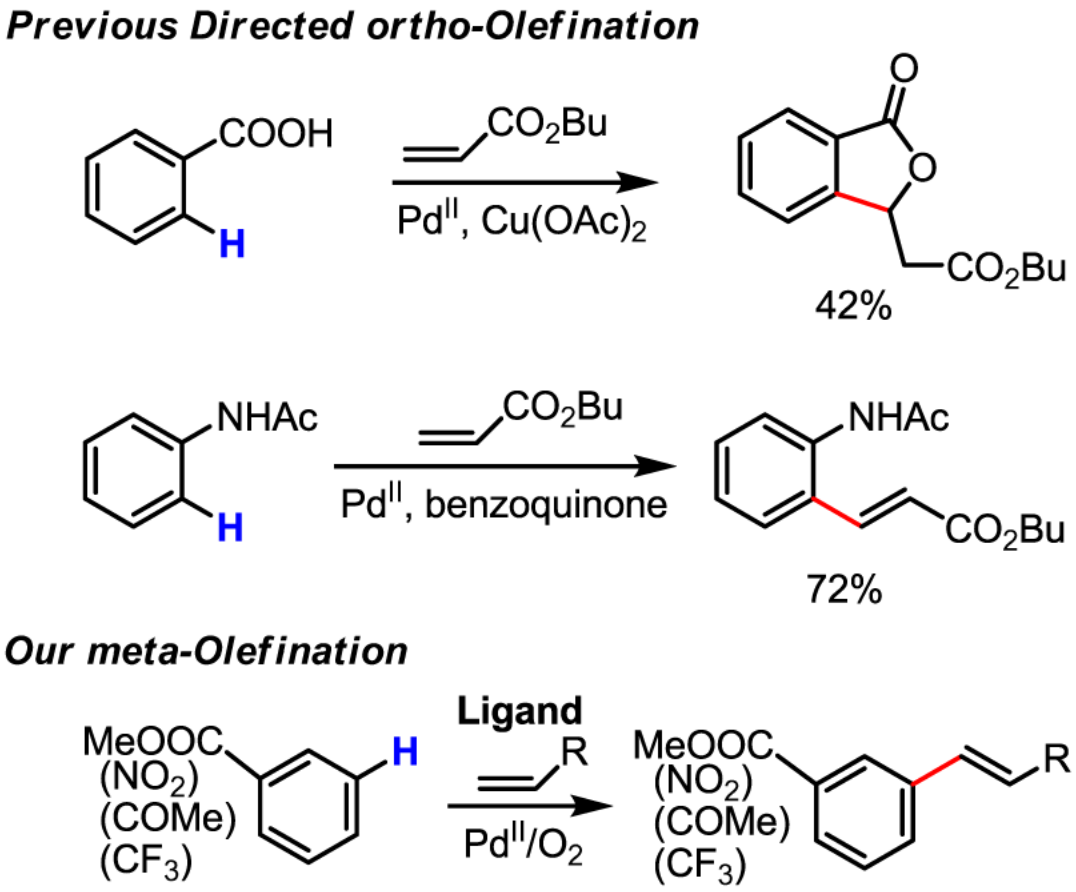
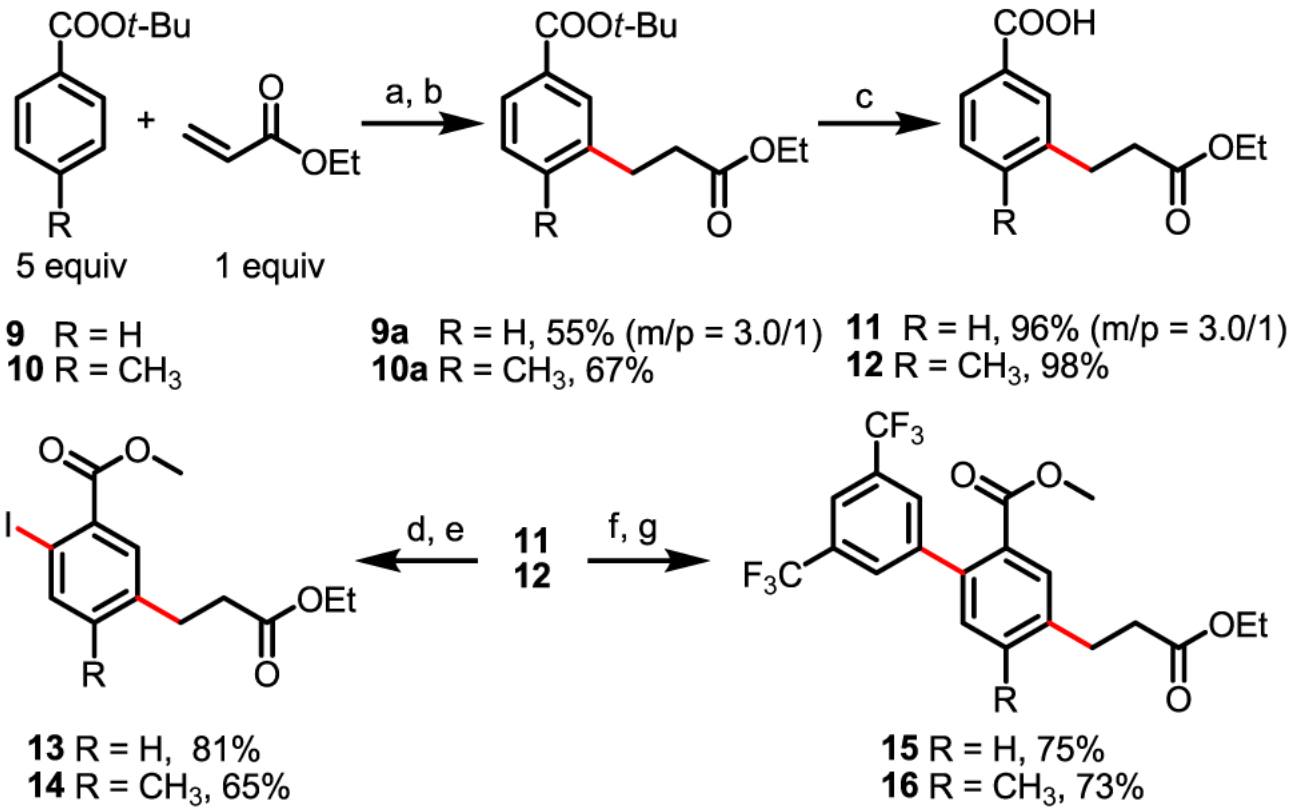


Scheme 1.
Pd-Catalyzed Olefination of Arenes



Scheme 2.

Synthesis of *tri*- and *tetra*-substituted Arenes

(a) $Pd(OAc)_2$ (10 mol%), **L3** (20 mol%), Ac_2O (1.5 equiv), EtOAc, 90 °C; (b) H_2, Pd/C, EtOAc; (c) TFA, DCM; (d) $PhI(OAc)_2$ (1.0 equiv), I_2 (1.0 equiv), $Pd(OAc)_2$ (10 mol%), Bu_4NI (1.0 equiv), DCE, 80 °C; (e) CH_2N_2; (f) $Pd(OAc)_2$ (10 mol%), ArI (3.0 equiv), AgOAc (1.5 equiv), AcOH (5.0 equiv), 120 °C; (g) CH_2N_2.

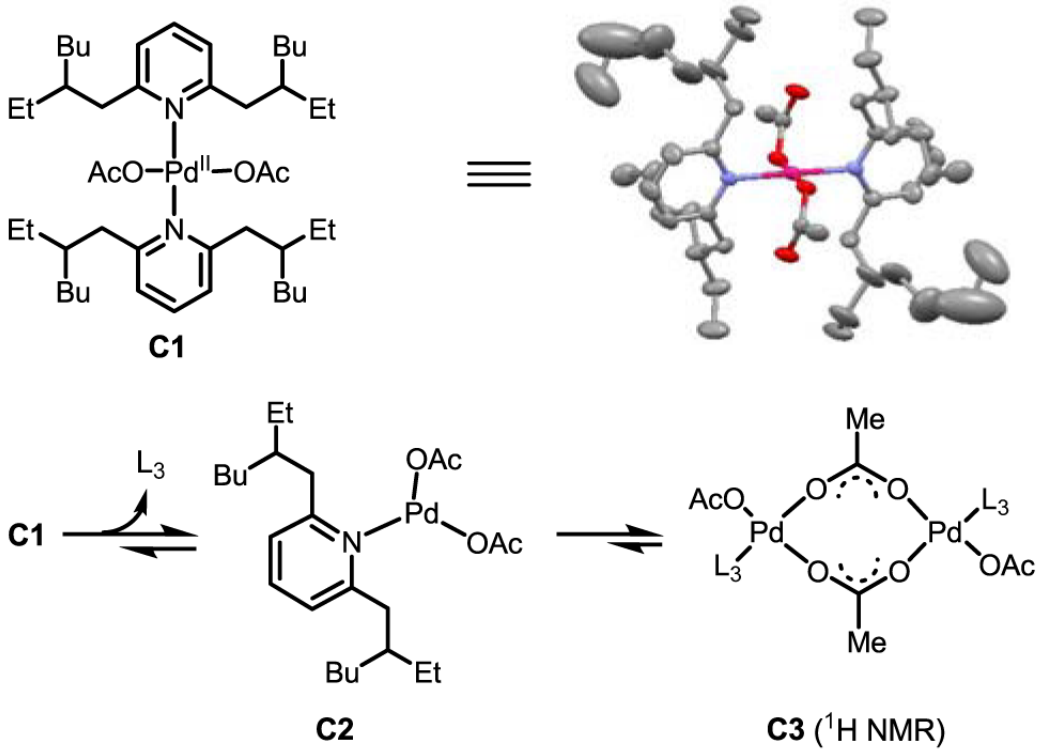
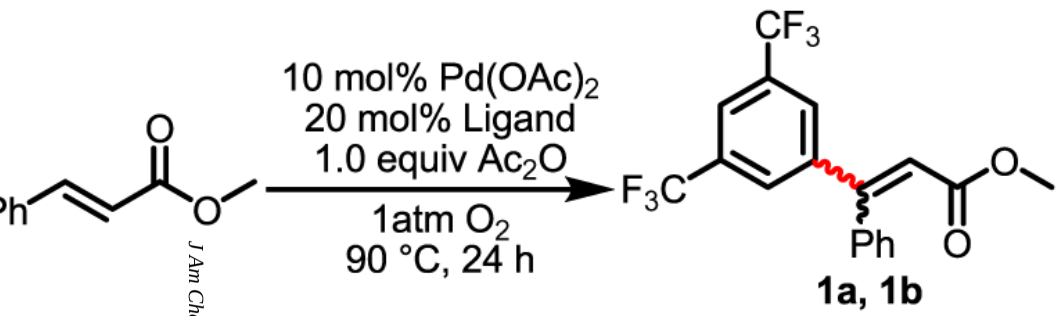
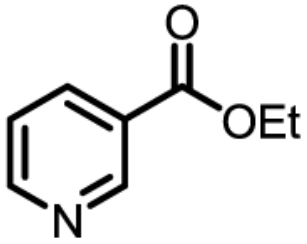


Figure 1.
Rapid Ligand Dissociation via a Mutual Repulsion



Yield (%)[b]	Entry	Ligand	Yield (%)[b]
<2	6		<5

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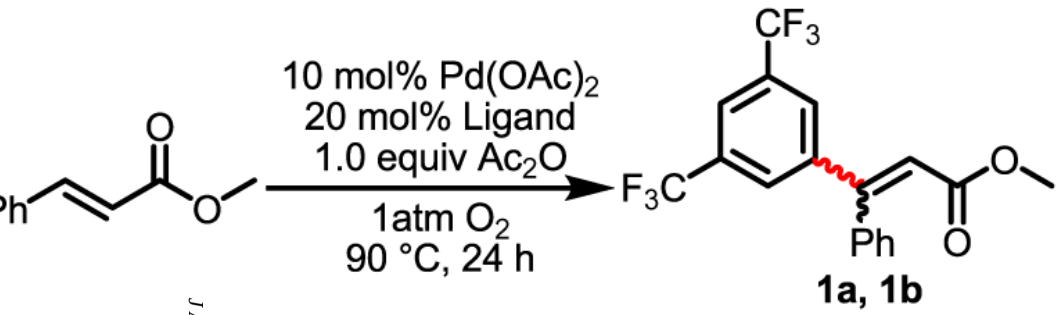
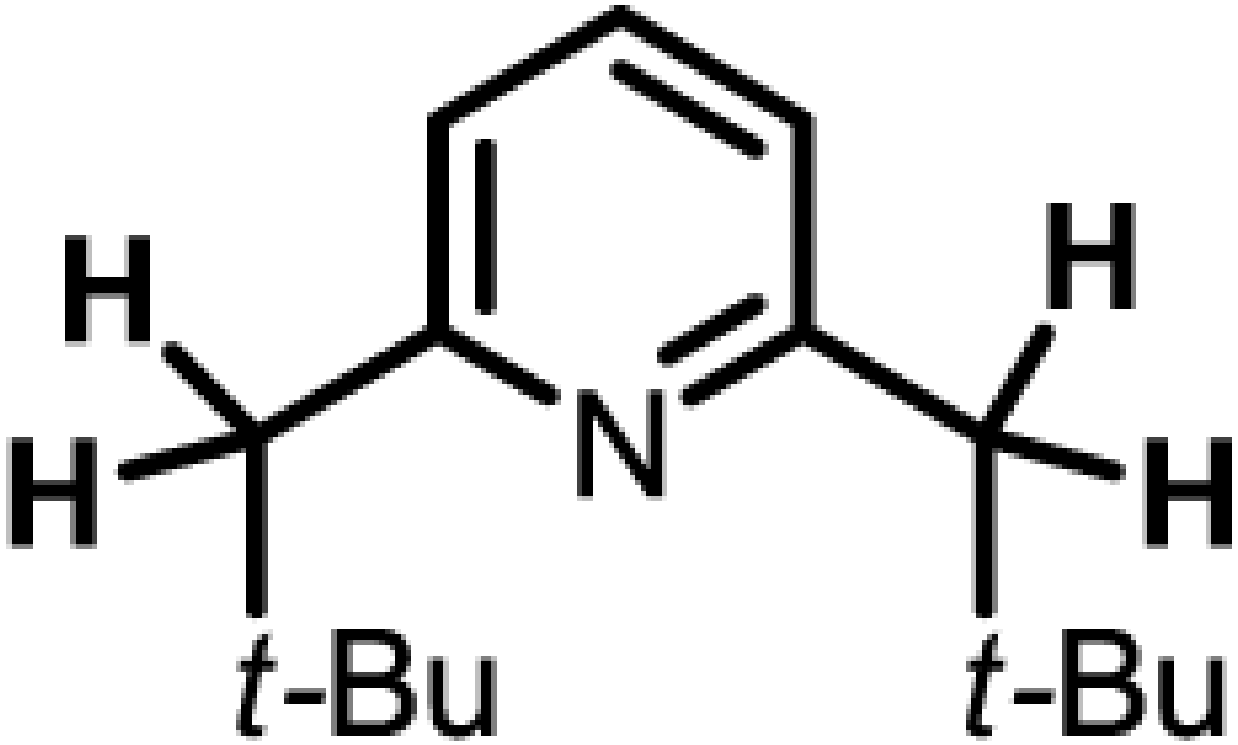


Yield (%)[b]	Entry	Ligand	Yield (%)[b]
<5	7		10

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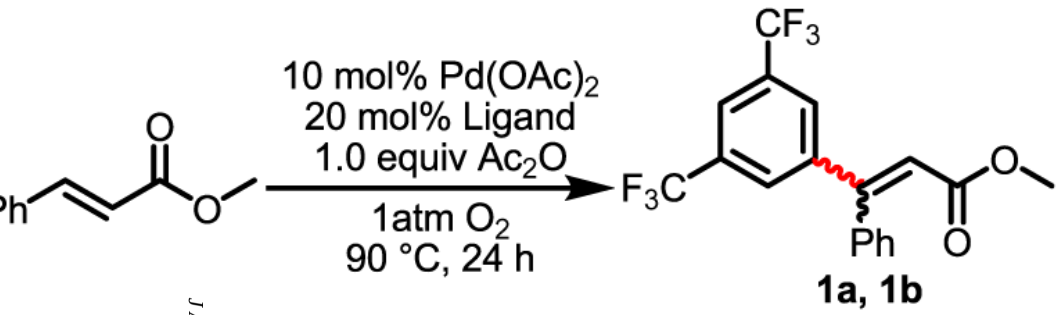
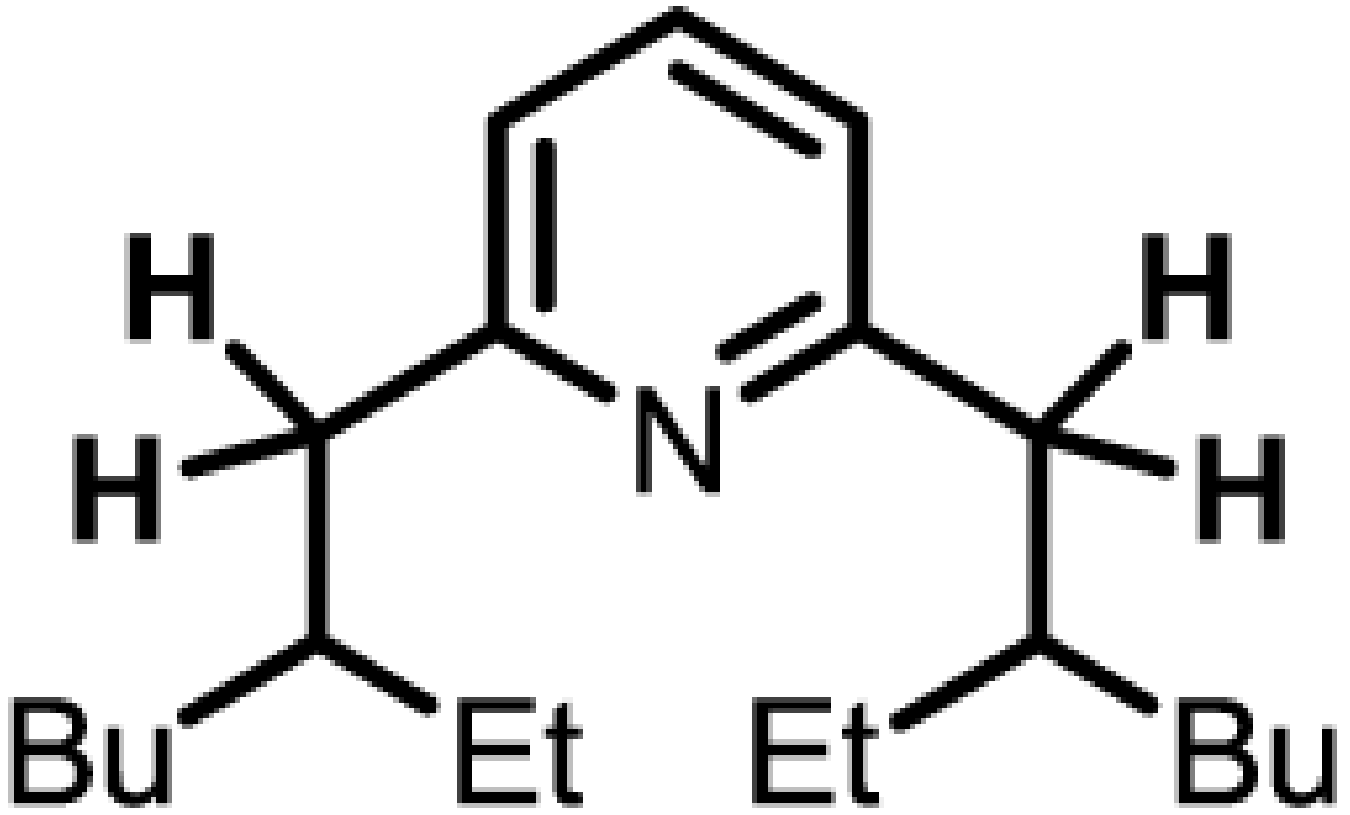
Entry	Ligand	Yield (%)[b]	Yield (%)[b]

Entry	Ligand	Yield (%)[b]
8	L2	<5
24 (E/Z=7.8)[c]	L2	<5



Yield (%)[b]	Entry	Ligand	Yield (%)[b]
<2	9		52 (E/Z=5.9)[c]

L3

Entry	Ligand	Yield (%)[b]	Yield (%)[b]

Table 2

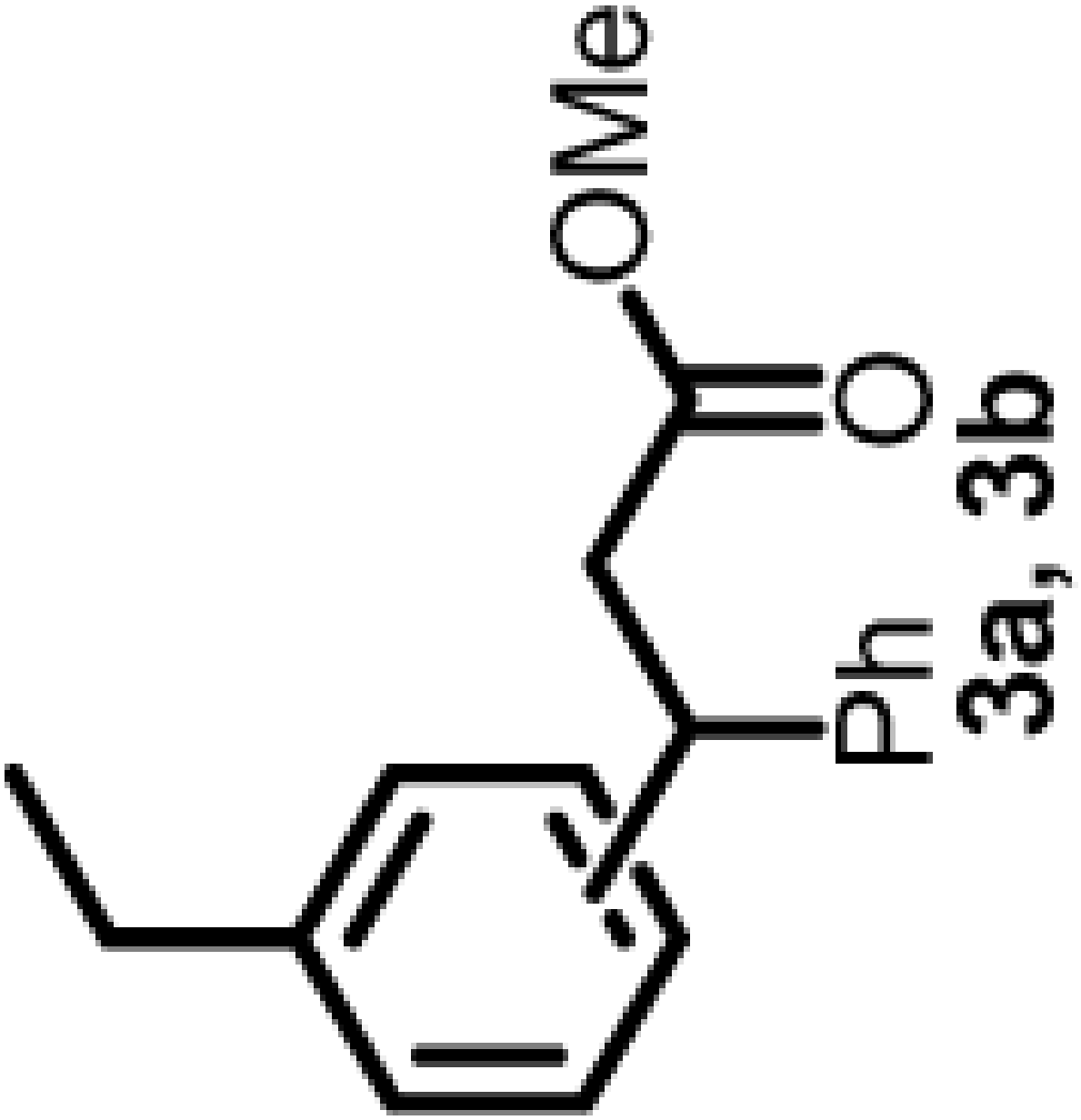
Product	Time (h)	Yield (%)[a]
1a, 1b	36	74 (E/Z = 85/15)

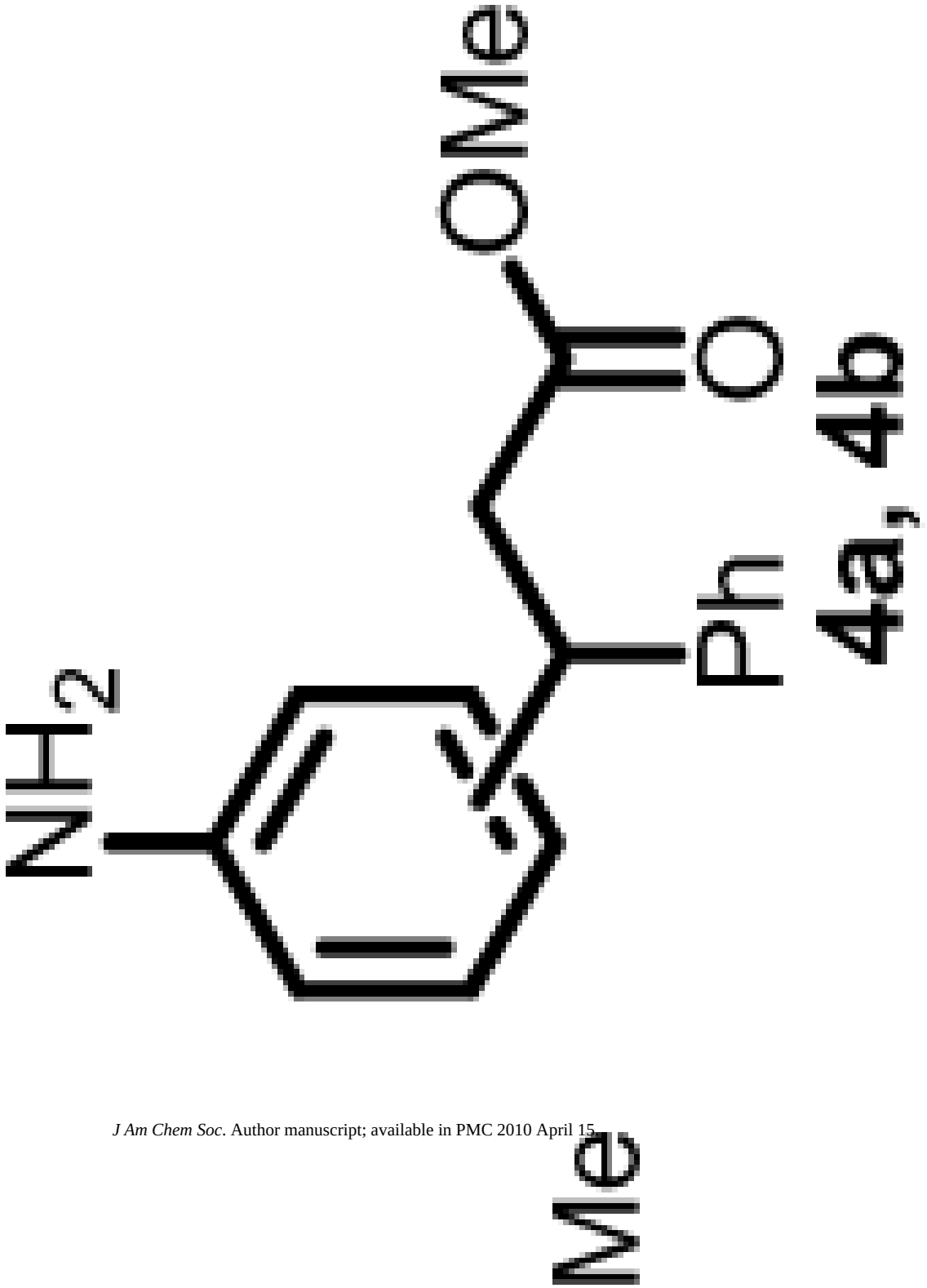
Product	Time (h)	Yield (%)[a]
1c	36	62

Product	Time (h)	Yield (%)[a]
2a, 2b	2	70 (m/p = 80/20) 58[c] (m/p = 78/22)

Product	Time (h)	Yield (%)[a]
2a, 2b	2	52 (m/p = 81/19)

Product	Time (h)	Yield (%)[a]
2c, 2d	24	81[e] (m/p = 79/21)

Product	Time (h)	Yield (%)[a]
 3a, 3b	60	65e (m/p =83/17)

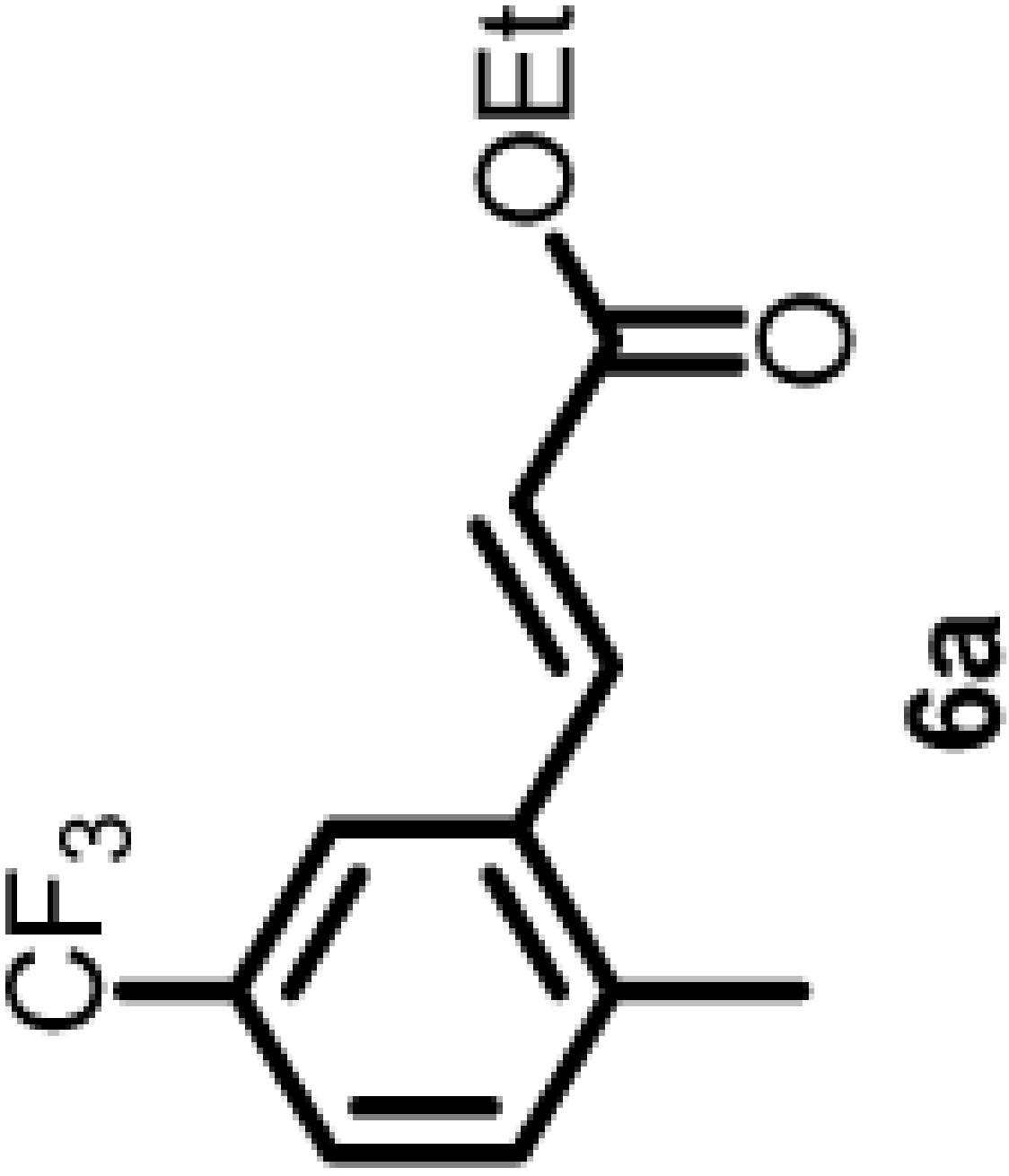
Product	Time (h)	Yield (%)[a]
 4a, 4b	16	73[e] (m/p = 84/16)

Product	Time (h)	Yield (%)[a]
5a, 5b	20	72 (m/p = 78/22)

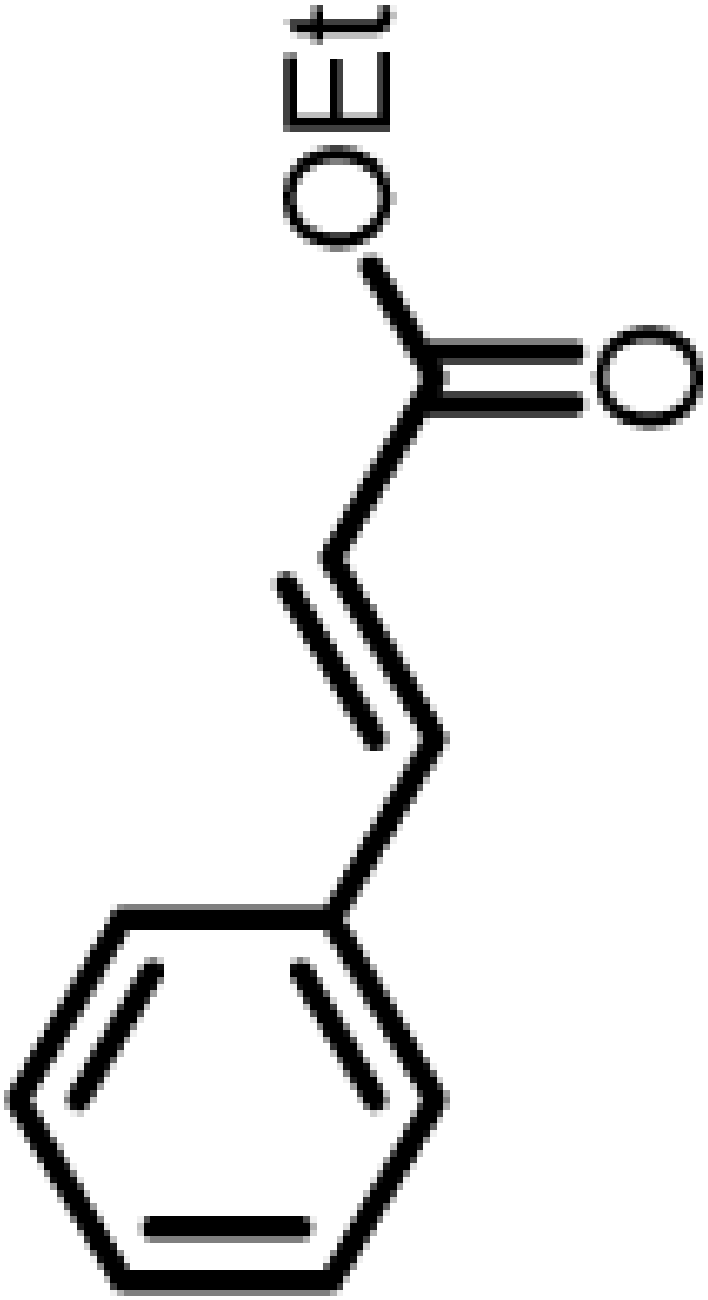
Product	Time (h)	Yield (%)[a]
5c, 5d	5	71 (m/p = 83/17)

Product	Time (h)	Yield (%)[a]
5e, 5f	56	70 (m/p = 78/22)

Product	Time (h)	Yield (%)[a]
5g, 5h	36	71 (m/p = 77/23)

Product	Time (h)	Yield (%)[a]
 6a	24	68

Product	Time (h)	Yield (%)[a]
7a	36	65[e, f]

Product	Time (h)	Yield (%)[a]
 8a	24	77

Product	Time (h)	Yield (%)[a]