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Palladium-Catalyzed Ring-Opening Coupling of Cyclobutenols with Aryl Halides

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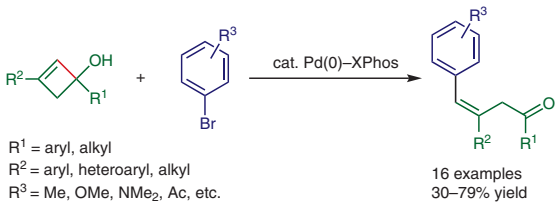

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Abstract A palladium(0)-catalyzed ring-opening cross-coupling reaction between *tert*-cyclobutenols and aryl halides produces γ-arylated β,γ-unsaturated ketones. In the case of aryl halides bearing functional groups at the *ortho* position, the resulting ring-opened ketones undergo intramolecular condensation to afford bicyclic aromatic compounds.

Key words palladium, cyclobutenols, arylation, ring opening, ketones, cross-coupling, condensation, homogeneous catalysis

The synthetic utility of transition-metal-catalyzed C–C bond-cleavage reactions has grown exponentially over the past two decades, enabling unique molecular transformations that are otherwise difficult to achieve.[1] Recently, transition-metal-catalyzed reactions of benzocyclobutenols have attracted considerable interest.[2] Such reactions encompass the formation of a transition-metal benzocyclobutenolate and subsequent β-carbon elimination involving selective C(sp^2)–C(sp^3) bond cleavage, which leads to an aryl transition-metal species bearing an *ortho*-acylmethyl substituent. In addition, the palladium-catalyzed cross-coupling reactions of aryl halides and the rhodium- and iridium-catalyzed annulations of alkynes, α,β-unsaturated ketones, and diazoesters have also been developed. However, studies into comparable reactions involving nonbenzofused analogues, i.e., cyclobutenols, are rare. In this context, in 2013, we reported a rhodium(I)-catalyzed alkyne insertion into cyclobutenols to afford tetrasubstituted benzenes.[3,4] Thus, we herein report the application of a previously developed palladium(0)-catalyzed ring-opening cross-coupling reaction using aryl halides to cyclobutenol substrates.[5] We expect that this coupling reaction will proceed via ring opening by selective C–C bond-cleavage to furnish γ-arylated β,γ-unsaturated ketones.

To examine the initial cross-coupling reaction between a cyclobutenol and an aryl halide, 1-butyl-3-phenylcyclobut-2-enol (**1a**) and 4-bromotoluene (**2a**, 1.2 equiv to **1a**) were reacted under the conditions employed for the coupling of benzocyclobutenols, i.e., $Pd_2(dba)_3$[6] (5 mol% Pd), DavePhos[6] (10 mol%), and Ag_2CO_3 (1.1 equiv) in toluene at 65 °C (Table 1, entry 1). The expected cross-coupling reaction produced the ring-opened arylated ketone **3a** in 32% NMR yield. We expect that this reaction proceeded via the oxidative addition of **2a** to palladium(0) to give arylpalladium(II) bromide **A** (see Table 1), subsequent ligand exchange of **A** with **1a** to yield arylpalladium(II) cyclobutenolate **B**, ring opening by β-carbon elimination with selective C(sp^2)–C(sp^3) bond cleavage[2,3,7] to afford alkenylpalladium(II) intermediate **C**, and finally, reductive elimination to yield the γ-arylated β,γ-unsaturated ketone **3a**.

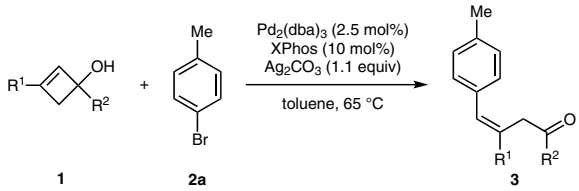
We then focused on optimization of the reaction conditions to improve the yield of **3a**. Interestingly, the use of XPhos[6] instead of DavePhos worked well in our case, affording **3a** in 62% NMR yield (Table 1, entry 2). In addition, an isolated yield of 79% was achieved when **2a** was used as the limiting reagent (Table 1, entry 3). In this case, **3a** was obtained as a 96:4 mixture of *E* and *Z* isomers in addition to a 9% yield of (*E*)-2-phenyl-2-octen-4-one (**4**), which arose from the thermal ring opening of **2a**.[8] The reaction performed with 4-iodotoluene afforded the desired product **3a** in 45% yield. Variation in the palladium/phosphine ratio from 1:2 to 1:1 led to a decrease in yield of **3a** (Table 1, entry 4). Although silver(I) oxide was successful as an effective additive, a slightly lower yield was obtained compared to other conditions (Table 1, entry 5). We also confirmed that the use of silver salts was not essential, as the reaction with *t*-BuOK also yielded **3a**; however, a significant quantity of **4** was also formed, thereby demonstrating the superiority of the silver salts in this reaction to yield the desired products **3** (Table 1, entry 6).[9] Furthermore, in the context of reaction temperature, the reaction performed at room temperature was slow and low yielding (7% yield), and the majority of starting material was recovered unchanged (Table 1, entry 7). In contrast, an increase in the reaction temperature to 110 °C resulted in significant competition from the thermal ring-opening reaction (Table 1, entry 8). With respect to the

reaction solvent, the use of 1,2-dichloroethane lowered the yield of **3a** to 24% (not shown in Table 1), while acetonitrile produced no reaction.

A range of cyclobutenols bearing different substituents were then subjected to the cross-coupling reaction with **2a** (Table 2).[10,11] The reaction of 1-butylcyclobutenols **1b** and **1c**, bearing *para*-substituted phenyl groups at the 3-position, afforded enones **3b** and **3c** in 61% and 70% yields, respectively (Table 2, entries 1 and 2). In addition, the coupling of 3-hexylcyclobutenol **1d** with **2a** gave **3d** in a moderate yield (42%, Table 2, entry 3), in contrast to the previous rhodium(I)-catalyzed reaction with alkynes, which resulted in exclusive thermal ring opening of the cyclobutenol without formation of the coupling product. 1,3-Diarylcyclobutenols (**1e** and **1f**) and the thiophene-bearing **1g** were also suitable coupling partners (38–60% yields, Table 2, entries 4–6).

The scope of aryl halides for the coupling reaction was also examined (Table 3). The reaction of **1a** and bromobenzene (**2b**) afforded enone **3h** in 50% yield (Table 3, entry 1), and various substituted phenyl halides **2c–h** gave rise to the

Table 2 Ring-Opening Cross-Coupling Reaction of Cyclobutenols **1** with 4-Bromotoluene (**2a**)[a]

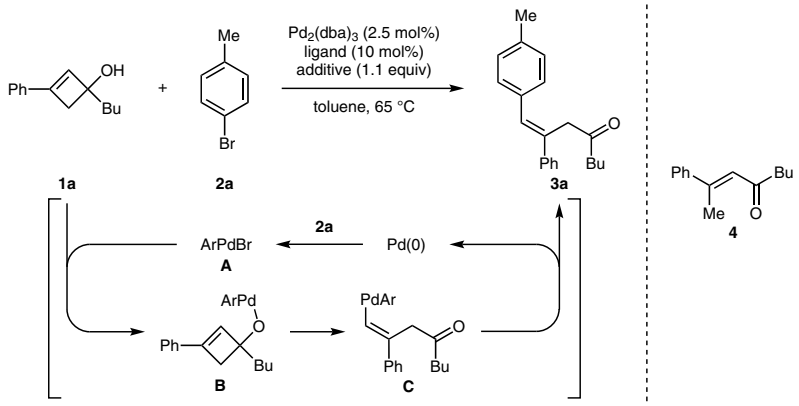


1 **2a** **3**

Entry	**1** R^1, R^2	Time (h)	**3** (%)[b]
1	**1b** 4-MeC_6H_4, Bu	11.5	**3b** 61
2	**1c** 4-MeOC_6H_4, Bu	10.5	**3c** 70
3	**1d** hexyl, Bu	16	**3d** 42
4	**1e** Ph, Ph	4	**3e** 60
5	**1f** Ph, 4-MeC_6H_4	6	**3f** 59
6	**1g** Ph, 2-thienyl	11.5	**3g** 38

[a] **1**, **2a** (**1**/**2a** = 1.2:1), $Pd_2(dba)_3$ (5 mol% Pd), XPhos (10 mol%), and Ag_2CO_3 (1.1 equiv) were heated at 65 °C in toluene.
[b] Isolated yield.

Table 1 Screening of the Reaction Conditions for the Ring-Opening Cross-Coupling of **1a** with **2a**[a]

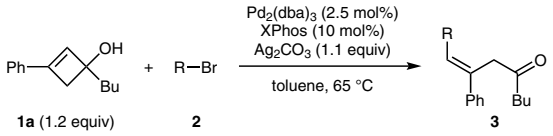


Entry	**1a**/**2a**	Ligand	Additive	Temp (°C)	**3a** (%)[b]	*E*/*Z*	**4** (%)[b]
1	1:1.2	DavePhos	Ag_2CO_3	65	32[c]		
2	1:1.2	XPhos	Ag_2CO_3	65	62[c]		
3	1.2:1	XPhos	Ag_2CO_3	65	79[d]	96:4	9
4	1.2:1	XPhos[e]	Ag_2CO_3	65	71[c]		
5	1.2:1	XPhos	Ag_2O	65	61[c]		
6	1.2:1	XPhos	*t*-BuOK	65	30		45
7	1.2:1	XPhos	Ag_2CO_3	r.t.	7[f]		
8	1.2:1	XPhos	Ag_2CO_3	110	44	62:38	39

[a] **1a**, **2a**, $Pd_2(dba)_3$ (5 mol% Pd), ligand (10 mol%), and additive (1.1 equiv) were heated in toluene for 4–8 h.
[b] Isolated yield unless otherwise noted.
[c] Yield determined by ^1H NMR spectroscopy.
[d] **3a** was isolated in 45% yield when the corresponding iodide was employed.
[e] 5 mol% XPhos was employed.
[f] 79% **1a** was recovered unreacted.

corresponding enones **3i–n** in 30–66% yields (Table 3, entries 2–7). In addition, 1-bromonaphthalene (**2i**) took part in the coupling reaction with **1a** (66% yield, Table 3, entry 8). Allyl bromide **2j** was also suitable as a coupling partner for the reaction with **1a**, providing dienone **3p** in 47% yield (Table 3, entry 9).

Table 3 Ring-Opening Cross-Coupling Reaction of 1-Butyl-3-phenylcyclobut-2-enol (**1a**) with Organohalides **2**[a]



1a (1.2 equiv) **2** **3**

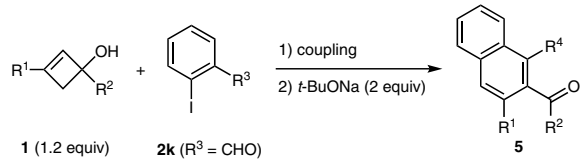
Entry	**2** R	Time (h)	**3** (%)[b]
1	**2b** Ph	14.5	**3h** 50
2	**2c** 4-MeOC$_6$H$_4$[c]	3	**3i** 59
3	**2d** 4-Me$_2$NC$_6$H$_4$	6	**3j** 39
4	**2e** 4-AcC$_6$H$_4$	6	**3k** 50
5	**2f** 3-MeC$_6$H$_4$	19	**3l** 66
6	**2g** 2-MeC$_6$H$_4$	28	**3m** 30
7	**2h** 3,5-Me$_2$C$_6$H$_3$	7	**3n** 49
8	**2i** 1-naphthyl	11.5	**3o** 66
9	**2j** allyl[d]	9	**3p** 47

[a] Unless otherwise noted, **1a**, **2** (**1a**/**2** = 1.2:1), $Pd_2(dba)_3$ (5 mol% Pd), XPhos (10 mol%), and Ag_2CO_3 (1.1 equiv) were heated at 65 °C in toluene.
[b] Isolated yield.
[c] The corresponding iodide was employed.
[d] **1a**/**2j** = 1:1.2.

Orellana previously reported that the reaction of benzocyclobutenols with aryl halides bearing electrophilic functional groups at the *ortho* position afforded phenanthrene products via condensation following the initial coupling reaction.[2a] Thus, we also examined the coupling/condensation sequence using cyclobutenols (Table 4).[12,13] Following the reaction of cyclobutenols **1a**, **1d**, and **1e** with 2-formyliodobenzene (**2k**) under the optimized conditions, the reaction mixture was treated with *t*-BuONa (2 equiv). An intramolecular aldol condensation then occurred to afford 2-acylnaphthalenes (**5a–c**) in 45–50% yields (Table 4, entries 1–3). Similarly, 2-cyanoiodobenzene (**2l**) reacted with the cyclobutenols to deliver 2-acyl-1-aminonaphthalenes **5d–f** via an analogous aromatization process (entries 4–6).[14]

In the reaction of 1,3-diphenylcyclobutenol (**1e**) with 2-iodoaniline (**2m**), the resulting enone spontaneously underwent intramolecular condensation to the expected seven-membered cyclic imine **6**, which was obtained in 43% yield. In contrast, surprisingly no trace of the corresponding

Table 4 Reaction of **1** with 2-Formyl- and 2-Cyanoiodobenzenes **2k** and **2l**[a]

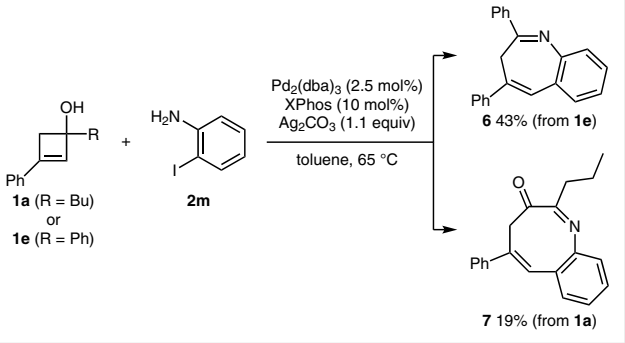


1 (1.2 equiv) **2k** (R^3 = CHO) **2l** (R^3 = CN) **5**

Entry	**1** R^1, R^2	**2** R^3	**5** R^4	Yield (%)[b]
1	**1a** Ph, Bu	**2k** CHO	**5a** H	46
2	**1d** hexyl, Bu	**2k**	**5b** H	45
3	**1e** Ph, Ph	**2k**	**5c** H	50
4	**1a**	**2l** CN	**5d** NH_2	59
5	**1d**	**2l**	**5e** NH_2	33
6	**1e**	**2l**	**5f** NH_2	52

[a] **1**, **2** (**1**/**2** = 1.2:1), $Pd_2(dba)_3$ (5 mol% Pd), XPhos (10 mol%), and Ag_2CO_3 (1.1 equiv) were heated at 65 °C in toluene for 13–21 h, then *t*-BuOK (2 equiv) was added and the mixture heated further for 2–4 h.
[b] Isolated yield.

seven-membered imine was obtained in the reaction of 1-butylcyclobutenol **1a** with **2m**; instead, intramolecular oxidative C=N bond formation took place to yield the eight-membered cyclic imine **7** (Scheme 1).[15]



Scheme 1 Reaction of cyclobutenols **1a** and **1e** with 2-aminoiodobenzene (**2m**)

In conclusion, we have described a method for the palladium-catalyzed arylation of cyclobutenols using aryl halides that involves ring opening of the cyclobutenols to yield a range of γ-arylated β,γ-unsaturated ketones. Furthermore, we also demonstrated that the products obtained from the reaction with aryl halides bearing functional groups at the *ortho* position could be transformed into bicyclic aromatic compounds through an intramolecular condensation reaction.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589117.

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(6) Abbreviations: dba = dibenzylideneacetone; DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

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(10) **General Procedure for Palladium(0)-Catalyzed Ring-Opening Cross-Coupling of *tert*-Cyclobutenols 1 with Organohalides 2 (GP-1)**

A mixture of $Pd_2(dba)_3$ (2.3 mg, 2.5 μmol), XPhos (4.7 mg, 9.9 μmol), cyclobutenol **1** (0.120 mmol), organohalide **2** (0.100 mmol), and Ag_2CO_3 (30.3 mg, 0.11 mmol) in toluene (0.50 mL) was heated at 65 °C with stirring. The reaction mixture was filtered through a plug of Florisil® washing with hexane/AcOEt (3:1), and the filtrate was concentrated. The residue was purified by preparative TLC on silica gel to afford ring-opened enone **3**.

(11) **Selected Data for Products**

(*E*)-1-(4-Methylphenyl)-2-phenyl-1-octen-4-one (3a)

The general procedure (GP-1) was followed using **1a** (24.3 mg, 0.120 mmol) and **2a** (17.1 mg, 0.100 mmol) for 6 h. Purification by preparative TLC on silica gel (hexane/AcOEt/toluene = 60:2:1, 4×) yielded **3a** (22.1 mg, 0.076 mmol, 76%) as a yellow oil. The *Z* isomer (1.0 mg, 0.003 mmol, 3%) and (*E*)-2-phenyl-2-octen-4-one (**4**, 2.1 mg, 0.010 mmol, 9%) were also isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.3 Hz, 3 H), 1.21 (sext, *J* = 7.5 Hz, 2 H), 1.44–1.51 (m, 2 H), 2.38 (t, *J* = 7.5 Hz, 2 H), 2.37 (s, 3 H), 3.78 (s, 2 H), 7.01 (s, 1 H), 7.15–7.22 (m, 4 H), 7.26–7.30 (m, 1 H), 7.33–7.38 (m, 2 H), 7.42–7.46 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 21.2, 22.2, 25.8, 42.2, 45.6, 126.2, 127.4, 128.45, 128.53, 129.1, 131.3, 134.6, 134.8, 137.0, 142.3, 209.1. IR: ν = 2954, 2931, 2870, 1712, 756, 702 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{21}H_{24}NaO$ [M + Na]$^+$: 315.1719; found: 315.1724.

(*E*)-4-(4-Methylphenyl)-1,3-diphenyl-3-buten-1-one (3e)

The general procedure (GP-1) was followed using **1e** (26.7 mg, 0.120 mmol) and **2a** (17.0 mg, 0.099 mmol) for 4 h. Purification by preparative TLC on silica gel (hexane/AcOEt = 60:1, 3×) yielded **3e** (18.6 mg, 0.060 mmol, 60%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 4.40 (s, 2 H), 7.11–7.15 (m, 3 H), 7.17–7.21 (m, 2 H), 7.23–7.28 (m, 1 H), 7.30–7.35 (m, 2 H), 7.43–7.49 (m, 4 H), 7.55–7.59 (m, 1 H), 7.94–7.98 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.2, 41.5, 126.2, 127.3, 128.2, 128.38, 128.43, 128.6, 129.1, 131.3, 133.2, 134.7, 134.8, 136.7, 136.9, 142.2, 197.9. IR: ν = 1682, 1327, 1211, 756, 694 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{20}NaO$ [M + Na]$^+$: 335.1406; found: 335.1410.

(*E*)-7-Phenyl-7,10-undecadien-5-one (3p)

The general procedure (GP-1) was followed using **1a** (20.2 mg, 0.100 mmol) and **2j** (14.6 mg, 0.121 mmol) for 9 h. Purification by preparative TLC on silica gel (hexane/AcOEt = 30:1, 3×) yielded **3p** (11.4 mg, 0.047 mmol, 47%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.5 Hz, 3 H), 1.20 (sext, *J* = 7.4 Hz, 2 H), 1.47 (quint, *J* = 7.5 Hz, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 2.88–2.95 (m, 2 H), 3.56 (s, 2 H), 5.02 (dd, *J* = 10.5, 1.0 Hz, 1 H), 5.09 (dd, *J* = 17.3, 1.2 Hz, 1 H), 5.85 (ddt, *J* =17.3,10.2, 6.1 Hz, 1 H), 5.96 (t, *J* = 7.5 Hz, 1 H), 7.18–7.32 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.2, 25.8, 33.2, 41.7, 45.0, 115.5, 126.0,

127.1, 128.4, 129.2, 134.2, 135.8, 142.2, 208.4. IR: ν = 2954, 1720, 756 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{17}H_{22}NaO$ $[M + Na]^+$: 265.1563; found: 265.1559.

(12) **General Procedure for Palladium(0)-Catalyzed Ring-Opening Cross-Coupling of tert-Cyclobutenols 1 with ortho-Functionalized Iodobenzenes 2 (GP-2)**

A mixture of $Pd_2(dba)_3$ (2.3 mg, 2.5 μmol), XPhos (4.7 mg, 9.9 μmol), cyclobutenol **1** (0.120 mmol), aryl iodide **2** (0.100 mmol), and Ag_2CO_3 (30.3 mg, 0.11 mmol), in toluene (0.50 mL) was heated at 65 °C with stirring. Then, *t*-BuOK (2 equiv) was added to the reaction mixture, and the mixture was further heated for 2–4 h. The reaction mixture was filtered through a plug of Florisil® washing with hexane/AcOEt (3:1), and the filtrate was concentrated. The residue was purified by preparative TLC on silica gel to afford naphthalene **4**.

(13) **Selected Data for Products**

2-Benzoyl-3-phenylnaphthalene (5c)

The general procedure (GP-2) was followed using **1e** (26.7 mg, 0.120 mmol) and **2k** (23.2 mg, 0.100 mmol) for 21 h. Purification by preparative TLC on silica gel (hexane/AcOEt = 20:1, 2×) yielded **5c** (15.3 mg, 0.050 mmol, 50%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.38 (m, 7 H), 7.42–7.47 (m, 1 H), 7.54–7.64 (m, 2 H), 7.70–7.73 (m, 2 H), 7.91–7.96 (m, 3 H), 8.04 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 126.8, 127.2, 127.8, 127.9, 128.1, 128.3, 128.4, 129.1, 129.2, 129.3, 130.0, 131.5, 132.8, 134.0, 137.4, 137.7, 138.5, 140.3, 198.3. IR: ν = 1666, 1281, 756, 694 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{16}NaO$ $[M + Na]^+$: 331.1093; found: 331.1096.

1-Amino-2-benzoyl-3-phenylnaphthalene (5f)

The general procedure (GP-2) was followed using **1e** (26.7 mg, 0.120 mmol) and **2l** (22.0 mg, 0.096 mmol) for 14 h. Purification by preparative TLC on silica gel (hexane/AcOEt = 30:1, 2×) yielded **5f** (16.3 mg, 0.050 mmol, 52%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.66 (br s, 2 H), 7.02–7.14 (m, 5 H), 7.21–7.30 (m, 4 H), 7.39–7.43 (m, 2 H), 7.53–7.58 (m, 1 H), 7.59–7.64 (m, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 116.5, 118.6, 121.6, 122.6, 125.6, 126.8, 127.6, 128.0, 128.1, 128.8, 129.1, 129.2, 131.7, 134.9, 139.9, 140.3, 141.9, 144.2, 200.4. IR: ν = 1604, 1273, 756, 694 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1383; found: 324.1380.

(14) Without the addition of a base, the reaction with aldehyde **2k** afforded naphthalene **5** in lower yields. In contrast, no condensation was observed in the reaction with nitrile **2l** in the absence of base.

(15) Further studies have been carried out to elucidate the details of this novel oxidative imination.