The Synthesis of Highly Functionalized 2-(2-Methylenecycloalkyl)pyrroles by Palladium-Catalyzed Cycloreduction

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Abstract: By utilizing the facile formation of an imine from an aldehyde and an amine, we have discovered a new and highly efficient Pd-catalyzed cycloreduction of enediynals leading to the corresponding 2-(2-methylenecycloalkyl)pyrroles in good to excellent yields.

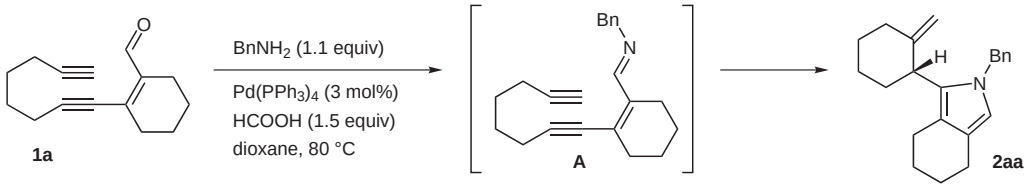
Key words: palladium, endiynal, pyrrole, catalyst, cycloreduction

Multicomponent and multistep one-pot methods to form complex molecules from structurally simple starting molecules is an important strategy in organic synthesis. Imines are versatile intermediates affording N-containing organic compounds and are easily formed from the corresponding aldehydes and primary amines. The Pd-catalyzed cycloreduction of enynes and enediynes gives various polycyclic compounds in a very convenient single step.[1] A major advantage of diyne cycloreduction is in the formation of stable alkenylpalladium intermediates while enyne cycloisomerization forms the labile alkylpalladium intermediates for β-elimination. Such an increase in stability of the intermediates has prompted us to further explore new reactions.[2] Recently we reported the highly functionalized and stereocontrolled synthesis of 2-(2-methylenecyclopentyl)furan derivatives by Pd-catalyzed cycloreduction. This strategy has been extended to imines to give the corresponding pyrroles.

N-Heterocyclic compounds have served as interesting building blocks in pharmaceutical and synthetic chemistry.[3] Among them, substituted pyrroles have been attracting increasing attention as synthetic target compounds due to their widespread occurrence in nature and due to the wide range of biological activities.[4] Our approach is a simple combination of classical imine formation and Pd-catalyzed cyclization. This idea came from the fact that the imine formation between aldehydes and primary amines occurs readily, even at room temperature, and Pd-catalyzed cycloreduction requires a higher temperature. Combining two reactions in a one-step process is important in terms of synthetic feasibility as well as atom economy.

Herein we report the highly efficient atom-economic synthesis of 2-(2-methylenecycloalkyl)pyrrole derivatives by a Pd-catalyzed cycloreduction of imines prepared in situ from the corresponding aldehydes (Scheme 1). Initially, we attempted Pd-catalyzed cycloreduction of **1a** in the presence of benzylamine and formic acid. When the aldehyde **1a** was mixed with benzylamine in dioxane at room temperature, the corresponding imine was formed almost exclusively based on the NMR of the reaction mixture. In a separate experiment, we know that the corresponding imine was cycloreduced under Pd catalysis. In fact, the pyrrole derivative **2aa** was isolated in good yield (85%) when $Pd(PPh_3)_4$ was employed as a catalyst in dioxane. The reaction could be carried out on gram-scale without loss of yield.

With this successful result, we have attempted to explore the scope of this method to synthesize a variety of structurally diverse pyrrole derivatives using a one-pot method. First, we selected six enediynals **1a**–**f** and four representative amines, benzylamine, ethylamine, aniline, and *n*-dodecylamine (Figure 1). The substrates **1a**, **1b**, and **1c** vary in the ring size of the tethers. The substrate **1d** has a *gem*-diester group which could help in the cyclization. The substrate **1e** has a TBSO-group and a stereogenic center and **1f** has a heteroatom, nitrogen, in the diyne group. The four amines include both aromatic and



Scheme 1 Pd-catalyzed cycloreduction of endiynal **1a** with benzylamine

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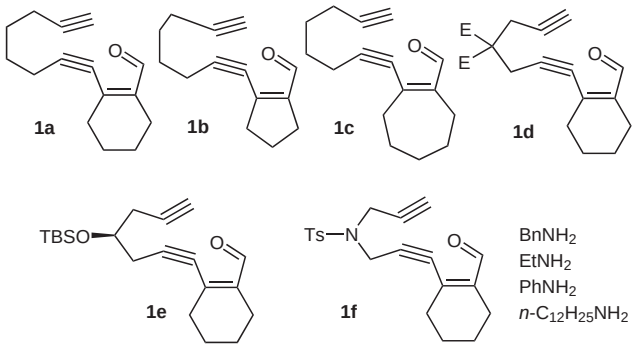


Figure 1 Representative endiynals **1a–f** and amines

aliphatic amines, which have different reactivities toward aldehydes. The enediynals **1a–f** were easily prepared by Sonogashira couplings of 2-bromocycloalkenecarboxaldehydes with diynes.

Since cycloreduction of these enediynals to the corresponding furan derivatives was successful, we postulated that complete imine formation prior to Pd-catalyzed cycloduction must be accomplished for the success of our multicomponent reactions. Thus, we initially focused on monitoring imine formation by looking at ^{1}H NMR spectra of the reaction solutions. Benzylamine rapidly reacted and aqueous ethylamine also reacted well with these enediynals. However, aniline required heating to complete the imine formation. We found that imine formations worked by mixing aldehydes **1a–f** and amines even in the presence of water. We attempted the one-pot multicomponent assembly by mixing enediynal, amine, Pd catalyst and formic acid in 1,4-dioxane. Our results are summarized in Table 1.[5]

All reactions were carried out under similar conditions except a few factors such as reaction temperatures and times. Overall, all attempted reactions were successful affording the corresponding pyrrole derivatives (Figure 2).

Cyclohexane-fused pyrroles **2aa–2ad** were synthesized in 70% to 85% yields (Table 1, entries 1–4). Cyclopentane-fused pyrroles were also synthesized in good yields (Table 1, entries 5–7).

To our surprise, aniline was also incorporated into the corresponding pyrroles, implying that imine formation with aniline was faster than cycloreduction of the enediynals. This strongly supports the fact that these cycloreductions can be achieved in a three-component reaction consisting

Table 1 Pd-Catalyzed Tandem Cycloreductions of Enediynals in the Presence of Amines[a]

Entry	Enynal	Amine	Temp (°C)	Time (h)	Product	Yield (%)
1	**1a**	$BnNH_2$	60	1	**2aa**	85
2	**1a**	$PhNH_2$	60	1	**2ab**	83
3	**1a**	$EtNH_2$	60	1	**2ac**	70
4	**1a**	n-$C_{12}H_{25}NH_2$	60	1	**2ad**	74
5	**1b**	$BnNH_2$	80	3	**2ba**	80
6	**1b**	$PhNH_2$	80	3	**2bb**	68[b]
7	**1b**	$EtNH_2$	80	3	**2bc**	56
8	**1c**	$BnNH_2$	80	1	**2ca**	71
9	**1c**	$PhNH_2$	80	1	**2cb**	62
10	**1c**	$EtNH_2$	80	1	**2cc**	41
11	**1d**	$BnNH_2$	80	3	**2da**	61
12	**1d**	$PhNH_2$	80	3	**2db**	71
13	**1d**	$EtNH_2$	80	3	**2dc**	68
14	**1e**	$BnNH_2$	80	1	**2ea**	81
15	**1e**	$PhNH_2$	80	1	**2eb**	76
16	**1e**	$EtNH_2$	80	1	**2ec**	69
17	**1f**	$BnNH_2$	80	1	**2fa**	66

[a] All reactions were carried out in one pot by mixing enediynal **1**, amine, Pd catalyst and formic acid in 1,4-dioxane. The reaction mixtures were stirred for 30 min at room temperature and then for the indicated time at the indicated temperatures.
[b] 10% of the corresponding furan was formed as a byproduct.

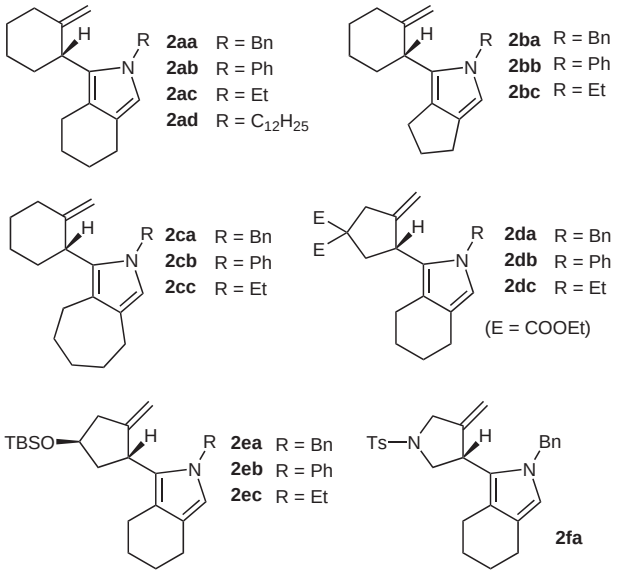
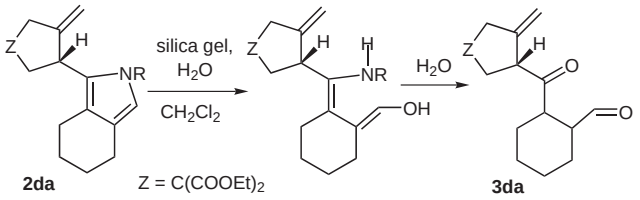


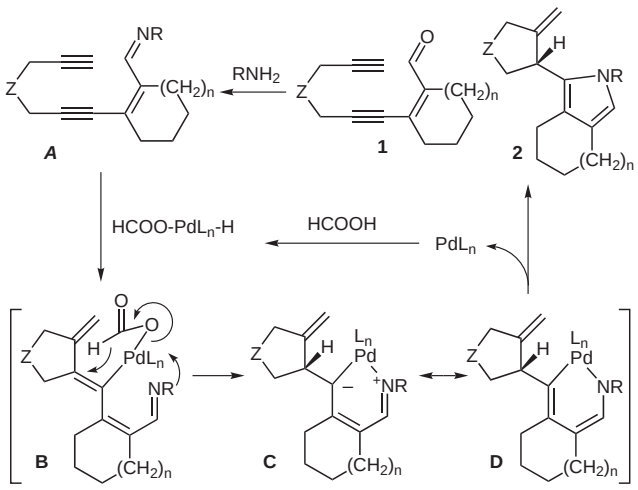
Figure 2 Pyrrole derivatives prepared in this study

of enediynal, amine and formic acid. Cycloheptane-fused pyrroles were synthesized in good yields (Table 1, entries 8 and 9). Enediynal **1d** bearing a *gem*-diester group underwent the reaction with benzylamine, ethylamine and aniline to give the corresponding methylenecyclopentyl-substituted pyrroles **2da**–**dc** in good yields. However, the pyrroles **2da**–**dc** were unstable and over a week gradually decomposed to the corresponding aldehydes, even at 0 °C (Scheme 2). The isolated pure product **2da** was subjected to a methylene chloride slurry of silica gel and stirred overnight at room temperature and the hydrolyzed product **3da** was isolated almost quantitatively.



Scheme 2 Silica gel mediated decomposition of **2da**

The TBS-containing enediynal **2e** afforded the pyrroles **2ea**–**ec** in high stereoselectivity along with their stereoisomers (less than 5%). Nitrogen-containing enediynal **2f** underwent the reaction with benzylamine to afford **2fa** in 66% yield. These reactions were understood to proceed in a similar manner as shown in Scheme 3. Enediynals **1** react with the corresponding amine to form imine **A**. The terminal triple bond of substrates **1** undergoes facile hydropalladation with a HPdOCOH species, generated in situ by mixing a Pd compound with HCOOH. This forms the vinylpalladium species which undergoes carbopalladation with the alkyne unit to form the intermediate **B**.[6] The imine nitrogen could then attack the palladium nucleus to release CO_2 and subsequently transfer hydride to the indicated carbon in **C** from the sterically less hindered



Scheme 3 Proposed mechanism for the formation of pyrroles

face.[7] Electron delocalization to **D** followed by reductive elimination results in the formation of the corresponding pyrrole **2** and PdL_n then reenters the next catalytic cycle.

In conclusion, we have discovered a new tandem multicomponent Pd-catalyzed cycloreduction of enediynals **1**, amines and formic acid leading to the corresponding 2-(2-methylenecycloalkyl)pyrrole derivatives **2** in good to excellent yields. Construction of complex molecules by combining all atoms of the reactants except CO_2 is both an atom-economical and an environmentally benign process. Due to the broad applications of pyrroles in the medicinal, synthetic and material chemistry fields, a convenient and atom-economical method for their synthesis is very useful to synthetic and medicinal chemists.

Acknowledgment

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References and Notes

(1) For reviews, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Lu, X.; Zhu, G.; Wang, Z.; Ma, S.; Ji, J.; Zhang, Z. *Pure Appl. Chem.* **1997**, *69*, 553.

(2) (a) Tsuji, J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; John Wiley: Chichester, **1995**. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, **1985**. (c) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; VCH: Weinheim, **1988**.

(3) Hölscher, M. *Green Chem.* **2004**, *6*, G75.

(4) (a) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (c) Bach, T.; Krüger, L. *Eur. J. Org. Chem.* **1999**, 2045. (d) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962. (e) Batna, A.; Spiteller, G. *Lipids* **1994**, *29*, 397. For reviews, see: (f) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, **1995**, 231–242. (g) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*, Vol. 14; Gribble, G. W.; Gilchrist, T. L., Eds.; Pergamon Press: Oxford, **2002**, 139–179.

(5) **General Experimental Procedure**: The substrates (enediynals **1**, 0.5mmol) in anhydrous dioxane (1.0 mL) were placed in a dry test tube. Then amine (1.2 equiv) was added to the reaction mixture using a microsyringe. The resultant solutions were stirred at r.t. for 30 min. To these solutions, $Pd(PPh_3)_4$ (3.0 mol%) and HCOOH (2 equiv) were added successively under an argon atmosphere. The reaction mixture was stirred for the time and temperature indicated in Table 1. Upon completion of the reactions, as monitored by TLC, the solvent was removed under reduced pressure and the products **2** were isolated by flash column chromatography as colorless oils in the indicated yields. Full characterization using ^{1}H NMR, ^{13}C NMR, IR and HRMS was performed.

2aa: IR (NaCl): 1709, 1675, 1646, 1499, 1445, 1391, 1318, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 3 H), 7.06 (d, *J* = 7.34 Hz, 2 H), 6.27 (d, *J* = 0.4 Hz, 1 H), 4.89 (ABq, Δδ = 10.6 Hz, *J* = 15.6 Hz, 2 H), 4.65 (s, 1 H), 4.24 (s, 1 H), 3.19 (t, *J* = 8.0 Hz, 1 H), 2.56 (m, 4 H), 2.37 (dd, *J* = 12.0, 2.0 Hz, 1 H), 1.98 (br t, *J* = 12.0 Hz, 1 H), 1.84–1.72 (m, 6 H), 1.69–1.60 (m, 2 H), 1.38–1.25 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.28, 139.10, 128.46, 127.83, 127.06, 126.80, 118.69, 116.95, 115.63, 107.57, 50.52, 42.44, 36.09, 32.72, 28.20, 27.38, 24.40, 24.03, 23.51, 22.35; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{22}H_{27}NK$: 344.1775; found: 344.1781.

2ab: IR (NaCl): 1598, 1501, 1445, 1385 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.33 (m, 2 H), 7.34–7.23 (m, 3 H), 6.49 (s, 1 H), 4.82 (d, *J* = 1.6 Hz, 1 H), 4.53 (q, *J* = 1.6 Hz, 1 H), 3.16 (dd, *J* = 12.0, 3.6 Hz, 1 H), 2.75–2.56 (m, 4 H), 2.43 (d, *J* = 12.8 Hz, 1 H), 2.00–1.77 (m, 7 H), 1.76–1.61 (m, 2 H), 1.44–1.24 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.48, 140.83, 128.75, 128.50, 126.38, 125.75, 119.89, 118.03, 116.35, 108.08, 42.48, 36.00, 32.59, 28.15, 27.13, 24.28, 24.00, 23.65, 22.23; HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{26}N$: 292.2065; found: 292.2039.

2ac: IR (NaCl): 1707, 1647, 1445, 1376, 1316 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 4.68 (s, 1 H), 4.21 (s, 1 H), 3.81–3.71 (m, 2 H), 3.30–3.21 (m, 1 H), 2.65–2.52 (m, 4 H), 2.50–2.44 (m, 1 H), 2.15–2.05 (m, 1 H), 1.99–1.84 (m, 4 H), 1.81–1.73 (m, 2 H), 1.70–1.62 (m, 2 H), 1.52–1.36 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.61, 127.48, 118.52, 116.68, 114.15, 107.76, 42.53, 41.54, 36.42, 32.97, 28.49, 27.74, 24.65, 24.29, 23.67, 22.55, 17.37; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{17}H_{25}NK$: 282.1624; found: 282.1615.

2ad: IR (NaCl): 1705, 1646, 1581, 1446, 1383, 1167 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (s, 1 H), 4.69 (d, *J* = 2.0 Hz, 1 H), 4.22 (d, *J* = 2.0 Hz, 1 H), 3.67 (m, 2 H), 3.24 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.62–2.52 (m, 4 H), 2.47 (d, *J* = 13.2 Hz, 1 H), 2.09 (td, *J* = 13.6, 3.2 Hz, 1 H), 1.98–1.84 (m, 4 H), 1.81–1.74 (m, 2 H), 1.71–1.59 (m, 4 H), 1.52–1.39 (m, 2 H), 1.34–1.23 (m, 21 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.20, 127.27, 118.00, 116.37, 114.81, 107.56, 46.86, 42.33, 36.20, 32.75, 31.90, 31.85, 29.64, 29.62, 29.58, 29.48, 29.33, 29.24, 28.27, 27.52, 26.89, 24.41, 24.06, 23.51, 22.68, 22.29, 14.11; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{27}H_{45}NK$: 422.3189; found: 422.3195.

2ba: IR (NaCl): 1644, 1496, 1443, 1350, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 3 H), 7.08–7.04 (m, 2 H), 6.24 (s, 1 H), 4.86 (s, 2 H), 4.67 (s, 1 H), 4.18 (s, 1 H), 3.10–3.02 (m, 1 H), 2.71–2.58 (m, 4 H), 2.42–2.35 (m, 1 H), 2.34–2.26 (m, 2 H), 2.03–1.93 (m, 2 H), 1.87–1.79 (m, 2 H), 1.78–1.69 (m, 1 H), 1.41–1.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.58, 139.57, 129.19, 128.79, 128.75, 127.90, 127.28, 126.97, 111.58, 107.37, 50.76, 42.49, 36.30, 33.57, 31.55, 28.89, 27.22, 26.74, 25.02; HRMS (ES): *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{25}KN$: 330.1624; found: 330.1629.

2bb: IR (NaCl): 1644, 1598, 1498, 1444, 1393, 1364 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.34 (m, 2 H), 7.31–7.27 (m, 3 H), 6.45 (s, 1 H), 4.76 (d, *J* = 1.6 Hz, 1 H), 4.40 (q, *J* = 1.6 Hz, 1 H), 3.10 (d, *J* = 13.2 Hz, 1 H), 2.73–2.63 (m, 4 H), 2.42–2.30 (m, 3 H), 1.95–1.87 (m, 2 H), 1.84–1.75 (m, 3 H), 1.41–1.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.54, 141.24, 130.53, 129.36, 129.01, 126.49, 126.42, 125.94, 112.34, 108.14, 42.32, 36.29, 34.02, 31.67, 28.74, 27.16, 26.45, 24.96; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{20}H_{23}KN$: 316.1468; found: 316.1462.

2bc: IR (NaCl): 1716, 1653, 1558, 1507, 1361 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 1 H), 4.65 (s, 1 H), 4.09 (s, 1 H), 3.70 (q, *J* = 7.2 Hz, 2 H), 3.14 (dd, *J* = 12.4, 2.0 Hz, 1 H), 2.56 (m, 4 H), 2.41 (br d, *J* = 13.2 Hz, 1 H), 2.31–2.23 (m, 2 H), 2.12–2.02 (m, 2 H), 1.94–1.85 (m, 2 H), 1.77 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1 H), 1.57–1.36 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.57, 128.91, 127.39, 125.11, 109.72, 107.37, 42.49, 41.38, 36.39, 33.64, 31.60, 28.95, 27.39, 26.71, 25.00, 17.43; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{16}H_{23}KN$: 230.1909; found: 230.1912.

2ca: IR (NaCl): 1670, 1644, 1600, 1520, 1494, 1447, 1390, 1349, 1332, 1169, 1119, 1075, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 3 H), 7.03 (d, *J* = 7.6 Hz, 2 H), 6.30 (s, 1 H), 4.91 (ABq, Δδ = 23.0 Hz, *J* = 16.0 Hz, 2 H), 4.68 (s, 1 H), 4.44 (s, 1 H), 3.21 (dd, *J* = 12.0, 4.0 Hz, 1 H), 2.53 (m, 4 H), 2.40 (d, *J* = 13.2 Hz, 1 H), 1.96 (td, *J* = 12.0, 2.0 Hz, 1 H), 1.85–1.70 (m, 4 H), 1.68–1.53 (m, 5 H), 1.36–1.22 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.14, 139.58, 129.44, 128.67, 127.25, 126.79, 125.34, 122.98, 117.57, 108.51, 50.90, 41.75, 36.46, 33.70, 33.60, 30.66, 30.03, 28.54, 28.24, 27.98, 27.63; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{23}H_{29}KN$: 358.1937; found: 358.1943.

2cb: IR (NaCl): 1643, 1598, 1518, 1445, 1389, 1326, 1171, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 7.30–7.20 (m, 3 H), 6.48 (s, 1 H), 4.83 (s, 1 H), 4.70 (s, 1 H), 3.20 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.70–2.52 (m, 4 H), 2.45 (d, *J* = 14.2 Hz, 1 H), 2.01–1.56 (m, 11 H), 1.46–1.22 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.84, 140.93, 129.82, 129.07, 126.70, 126.44, 125.86, 124.08, 117.97, 108.88, 42.24, 36.38, 33.66, 33.53, 30.38, 29.62, 28.45, 28.32, 28.04, 27.41; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{22}H_{27}KN$: 344.1781; found: 344.1782.

2cc: IR (NaCl): 1700, 1645, 1520, 1446, 1389, 1321, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (s, 1 H), 4.71 (d, *J* = 2.0 Hz, 1 H), 4.40 (q, *J* = 2.0 Hz, 1 H), 3.75 (m, 2 H), 3.27 (br d, *J* = 12.0 Hz, 1 H), 2.59–2.45 (m, 5 H), 2.15–2.05 (m, 1 H), 1.93–1.83 (m, 3 H), 1.82–1.73 (m, 3 H), 1.65–1.54 (m, 4 H), 1.48–1.37 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.31, 128.79, 124.82, 122.42, 115.77, 108.44, 41.73, 41.56, 36.52, 33.65, 33.56, 30.53, 29.95, 28.49, 28.14, 28.02, 27.73, 17.32; HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{18}H_{27}KN$: 296.1781; found: 296.1777.

2da: IR (NaCl): 1730, 1496, 1445, 1388, 1366, 1298, 1262, 1247, 1186, 1155, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 3 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 6.32 (s, 1 H), 4.97 (s, 2 H), 4.94 (d, *J* = 2.0 Hz, 1 H), 4.65 (q, *J* = 2.0 Hz, 1 H), 4.16 (m, 4 H), 3.82 (br t, *J* = 8.8 Hz, 1 H), 3.06 (m, 2 H), 2.55 (br s, 2 H), 2.48–2.34 (m, 3 H), 2.16 (t, *J* = 12.8 Hz, 1 H), 1.70 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.86, 171.60, 148.70, 139.08, 128.81, 127.42, 126.86, 126.28, 119.28, 117.57, 116.53, 108.22, 61.69, 58.52, 50.90, 40.55, 40.35, 39.87, 24.29, 24.20, 22.96, 22.40, 14.23, 14.21; HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{33}NaNO_4$: 458.2307; found: 458.2314.

2db: IR (NaCl): 1731, 1598, 1500, 1386, 1348, 1187, 1071, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m,

2 H), 7.36–7.26 (m, 3 H), 6.48 (s, 1 H), 5.00 (d, *J* = 2.8 Hz, 1 H), 4.75 (q, *J* = 2.8 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.14–4.04 (m, 2 H), 3.78 (m, 1 H), 3.05 (m, 2 H), 2.66–2.60 (m, 2 H), 2.59 (dd, *J* = 12.8, 7.6 Hz, 1 H), 2.55–2.39 (m, 2 H), 2.32 (t, *J* = 12.8 Hz, 1 H), 1.74 (m, 4 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.75, 171.63, 149.21, 140.69, 129.18, 127.11, 127.03, 126.47, 120.45, 118.16, 117.20, 108.06, 61.75, 61.66, 58.58, 40.88, 40.32, 39.87, 24.20, 24.14, 23.01, 22.35, 14.26, 14.14; HRMS: *m*/*z* $[M + K]^+$ calcd for $C_{26}H_{31}KNO_4$: 460.1890; found: 460.1898.

2dc: IR (NaCl): 1730, 1446, 1377, 1298, 1186, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (s, 1 H), 5.00 (d, *J* = 2.4 Hz, 1 H), 4.70 (d, *J* = 2.4 Hz, 1 H), 4.30–4.17 (m, 4 H), 3.92 (m, 1 H), 3.80 (q, *J* = 7.2 Hz, 2 H), 3.15 (m, 2 H), 2.67 (dd, *J* = 12.8, 7.6 Hz, 1 H), 2.55 (br s, 2 H), 2.47–2.32 (m, 2 H), 2.25 (t, *J* = 12.6 Hz, 1 H), 1.69 (m, 4 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.84, 171.42, 148.75, 125.28, 118.69, 116.76, 114.52, 107.86, 61.55, 58.34, 41.48, 40.34, 40.10, 39.81, 24.09, 23.99, 22.65, 22.13, 21.37, 19.93, 17.18, 14.04; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{31}NaNO_4$: 396.2151; found: 396.2154.

2ea: IR (NaCl): 1705, 1472, 1389, 1252, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 3 H), 7.10–7.05 (m, 2 H), 6.28 (s, 1 H), 4.98 (s, 2 H), 4.87 (s, 1 H), 4.62 (s, 1 H), 4.10 (m, 1 H), 3.58 (m, 1 H), 2.68 (dd, *J* = 16.0, 7.2 Hz, 1 H), 2.56 (m, 2 H), 2.47 (m, 2 H), 2.42–2.34 (m, 1 H), 1.94 (m, 1 H), 1.77 (dd, *J* = 12.4, 6.8 Hz, 1 H), 1.73–1.68 (m, 4 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.72, 139.00, 128.49, 127.16, 126.75, 118.87, 117.00, 115.88, 107.46, 71.71, 50.67, 42.50, 41.89, 39.14, 25.86, 24.12, 24.04, 22.67, 22.19, –4.71, –4.76; HRMS: *m*/*z* $[M + K]^+$ calcd for $C_{27}H_{39}KNOSi$: 460.2438; found: 460.2434.

2eb: IR (NaCl): 1598, 1500, 1386, 1251, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 2 H), 7.35–7.23 (m, 3 H), 6.45 (s, 1 H), 4.92 (d, *J* = 1.2 Hz, 1 H), 4.72 (q, *J* = 1.2 Hz, 1 H), 4.08 (m, 1 H), 3.52 (m, 1 H), 2.72–2.60 (m, 4 H), 2.54 (s, 1 H), 2.42–2.31 (m, 1 H), 2.06 (m, 1 H), 1.91 (td, *J* = 12.4, 9.2 Hz, 1 H), 1.82–1.69 (m, 4 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.49, 140.71, 128.94, 127.75, 126.69, 126.25, 120.17, 117.67, 116.53, 107.17, 71.57, 42.28, 41.68, 39.51, 25.86, 23.99, 23.96, 22.84, 22.16, 18.12, –4.67, –4.70; HRMS: *m*/*z* $[M + K]^+$ calcd for $C_{26}H_{37}NaNOSi$: 430.2542; found: 430.2546.

2ec: IR (NaCl): 1710, 1658, 1471, 1376, 1252, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (s, 1 H), 4.91 (s, 1 H), 4.64 (s, 1 H), 4.26 (m, 1 H), 3.81 (q, *J* = 7.2 Hz, 2 H), 3.67 (m, 1 H), 2.76 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.57 (br s, 2 H), 2.46 (br s, 2 H), 2.42 (m, 1 H), 2.21 (m, 1 H), 1.88 (td, *J* = 12.4, 9.0 Hz, 1 H), 1.71 (m, 4 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.48, 126.47, 118.77, 116.80, 114.32, 107.45, 72.06, 42.73, 42.12, 41.57, 39.31, 26.12, 24.41, 24.32, 22.76, 22.41, 18.43, 17.24, –4.42, –4.46; HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{38}NOSi$: 360.2723; found: 360.2724.

2fa: IR (NaCl): 1705, 1597, 1495, 1453, 1387, 1346, 1163, 1094, 1041, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.8 Hz, 2 H), 7.32–7.24 (m, 5 H), 6.95–6.92 (m, 2 H), 6.32 (s, 1 H), 4.90 (d, *J* = 2.4 Hz, 1 H), 4.86 (s, 2 H), 4.61 (q, *J* = 2.4 Hz, 1 H), 4.05 (br d, *J* = 14.0 Hz, 1 H), 3.82 (m, 1 H), 3.78–3.70 (m, 1 H), 3.49 (t, *J* = 9.0 Hz, 1 H), 2.95 (t, *J* = 9.0 Hz, 1 H), 2.51 (t, *J* = 6.0 Hz, 2 H), 2.42 (s, 3 H), 2.22–2.12 (m, 1 H), 1.95 (dt, *J* = 15.6, 6.4 Hz, 1 H), 1.71–1.61 (m, 2 H), 1.61–1.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.73, 143.62, 138.44, 132.34, 129.60, 128.65, 127.78, 127.43, 126.22, 122.58, 119.19, 118.20, 117.26, 108.08, 52.34, 52.14, 50.70, 40.22, 23.86, 23.78, 22.63, 21.96, 21.53; HRMS (ES+): *m*/*z* $[M + K]^+$ calcd for $C_{27}H_{30}KN_2$: 421.2046; found: 421.2050.

(6) For reviews, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.

(7) H-Transfer of the β-carbon to the Pd intermediate has not been reported. We thought that the imine nitrogen could attack the Pd and then concomitant electron moving might lead to H-transfer to the β-carbon, and further delocalization to the palladacycle **D** in Scheme 3. For more discussion, see: Oh, C. H.; Park, H. M.; Park, D. I. *Org. Lett.* **2007**, *9*, 1191.