Lewis Acid Catalyzed Benzylic C–H Bond Functionalization of Azaarenes; Addition to Imines and Enones

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Abstract: Lewis acid catalyzed benzylic C–H bond functionalization of alkyl-substituted azaarenes is described. The addition to *N*-tosyl imines proceeded under solvent-free conditions using various Lewis acids. $Cu(OTf)_2$ was the best Lewis acid, and 1,2-addition proceeded at 60–120 °C, giving products in 23–92% yield. On the other hand, strongly Lewis acidic rare-earth metal triflates, $Sc(OTf)_3$ and $Y(OTf)_3$, were essential to promote the 1,4-addition of alkyl-substituted azaarenes to enones, and products were obtained in 60–96% yield.

Key words: nitrogen heterocycles, C–H bond functionalization, enones, imines, Lewis acids

Metal-catalyzed C(sp^3)-H bond functionalizations are valuable methods in organic synthesis.[1,2] Among them, C(sp^3)-H bond activation/C–C bond-forming reactions of azaarenes, such as pyridines, pyrimidines, quinolines, and isoquinolines, provide straightforward access to useful building blocks for the design and synthesis of biologically active compounds. To realize the C(sp^3)-H bond functionalization of alkyl-substituted azaarenes, transition-metal-catalyzed chelation-assisted methods for C–C bond formation have been investigated by many groups.[3] Further studies to expand the reaction scope for the synthesis of diverse sets of functionalized azaarenes by enabling the use of various coupling partners are desirable. To complement transition-metal-catalyzed processes, Lewis acid catalyzed couplings of alkyl-substituted azaarenes have recently been investigated by Huang et al., Rueping et al., and other groups.[4,5] We also communicated our preliminary results on the utility of rare-earth metal triflate for the addition of 2-methyl-azaarenes to enones.[5] In this manuscript, we report full details of our efforts on Lewis acid catalyzed benzylic C(sp^3)-H bond functionalization of alkyl-substituted azaarenes **1** (Figure 1); $Cu(OTf)_2$-catalyzed addition to imines, and $Sc(OTf)_3$ and $Y(OTf)_3$ catalyzed addition to enones will also be discussed.

On the basis of precedents in Lewis acid catalyzed intramolecular C(sp^3)-H functionalization,[6–12] Lewis acid assisted C(sp^2)-H functionalization of pyridines and/or quinolines,[13] as well as our ongoing projects on acid/base-catalyzed proton transfer processes,[14] we envisioned the use of a Lewis acid for the functionalization of *ortho*-methyl-substituted azaarenes under proton transfer conditions. Our working hypothesis is shown in Scheme 1. Activation of azaarenes by the coordination to a strong Lewis acid would increase the acidity of benzylic C–H bonds. Cleavage of the C–H bond by either an external base (i.e., azaarene **1**) or counterions of a Lewis acid would generate a metal enamide species.[15] The addition of the metal enamide to electrophiles, such as imines or enones, would generate a metal-amide or an enolate intermediate, which would afford the product upon protonation. In addition to the *ortho*-methyl group activation, we envisioned that the strategy might also be applicable to compounds with a *para*-methyl group by using the azaarene as an external base.

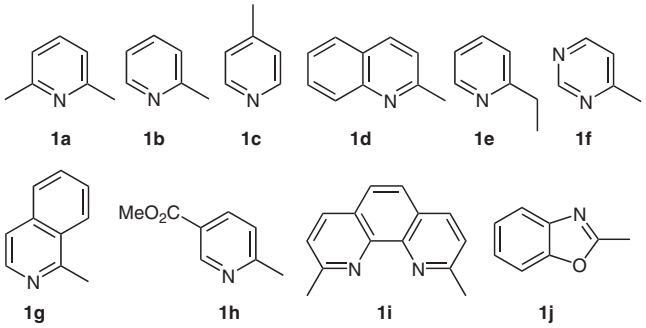
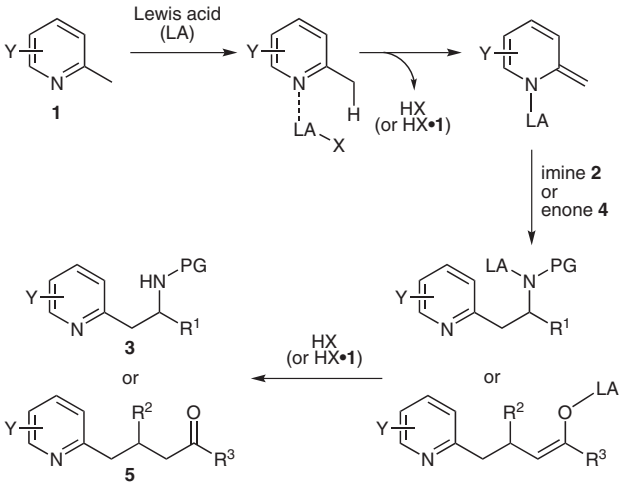


Figure 1 Structures of alkyl-substituted azaarenes **1a**–**i** and benzoxazole **1j**



Scheme 1 Working hypothesis for Lewis acid catalyzed C–H functionalization of methyl-substituted azaarenes with imines and enones

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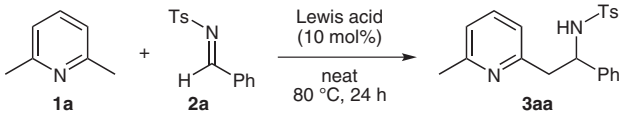
To test the feasibility of our hypothesis, lutidine **1a** and tosyl-imine **2a** were selected as model substrates. In the previous reports on Lewis acid catalyzed addition of lutidine to imines,[4] relatively high temperature (120 °C) was often required to efficiently promote the reaction. Initial attempts to promote the reaction at lower temperature revealed that solvent-free conditions with excess lutidine **1a** (10 equiv) was suitable. As shown in Table 1, various Lewis acids promoted the model reaction in moderate to good yield at 80 °C. Among the metals screened, $Mg(OTf)_2$, $Zn(OTf)_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$ gave product **3aa** in more than 80% yield after 24 hours; the best reactivity was observed with $Cu(OTf)_2$ (90% isolated yield; Table 1, entry 8). Other less Lewis acidic copper sources resulted in poor reactivity (Table 1, entries 9 and 10); thus $Cu(OTf)_2$ was selected as the best catalyst for the addition of azaarenes **1** to imines **2**.

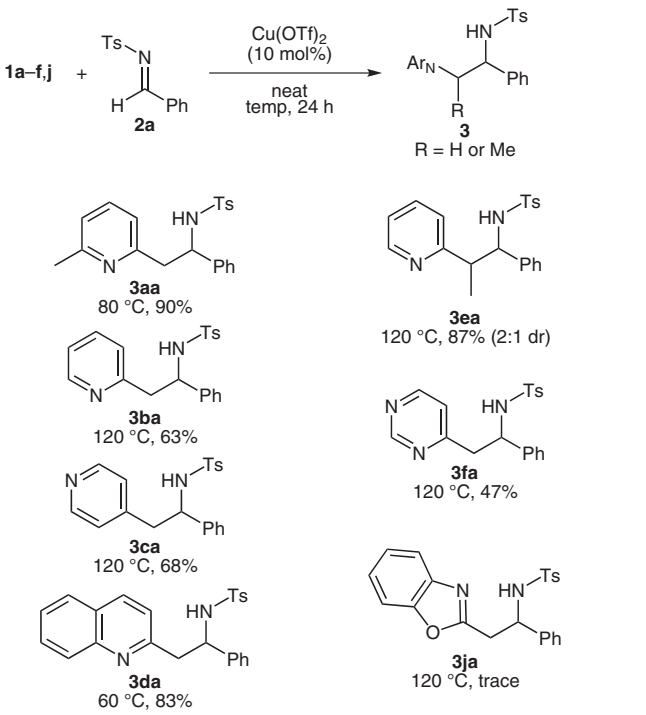
Table 1 Effect of Lewis Acid on the Addition of Lutidine **1a** to Imine **2a**



Entry	Lewis acid	Yield (%)[a]
1	$Mg(OTf)_2$	84
2	$Al(OTf)_3$	56
3	$In(OTf)_3$	75
4	$Fe(OTf)_3$	68
5	$Zn(OTf)_2$	86
6	$Bi(OTf)_3$	84
7	$Sc(OTf)_3$	87
8	$Cu(OTf)_2$	90[b]
9	$Cu(OAc)_2$	34
10	CuOTf·0.5PhMe	35

[a] Determined by ^{1}H NMR analysis.
[b] Isolated yield after purification by column chromatography.

The substrate scope and limitations of donors are summarized in Scheme 2. Benzylic C(sp^3)-H bond activation of methyl-substituted pyridines, quinoline, and pyrimidine proceeded smoothly. 2-Picoline (**1b**) was less reactive than **1a**, and higher reaction temperature (120 °C) was required to obtain **3ba** in 63% yield. As expected, the present method was applicable to 4-picoline (**1c**), and **3ca** was obtained in 68% yield. 2-Methylquinoline (**1d**) showed good reactivity even at 60 °C, giving **3da** in 83% yield after 24 hours. With 2-ethylpyridine (**1e**) and 4-methylpyrimidine (**1f**), the reactions were run at 120 °C, and products were obtained in 87 and 47% yield, respectively. On the other hand, only trace amounts, if any, product **3ja** was obtained with benzoxazole. As shown in Scheme 3, addition of **1a** to various imines proceeded smoothly at 80 °C, except for the less reactive 4-methoxy-substituted imine, to give products in 76–92% yield.

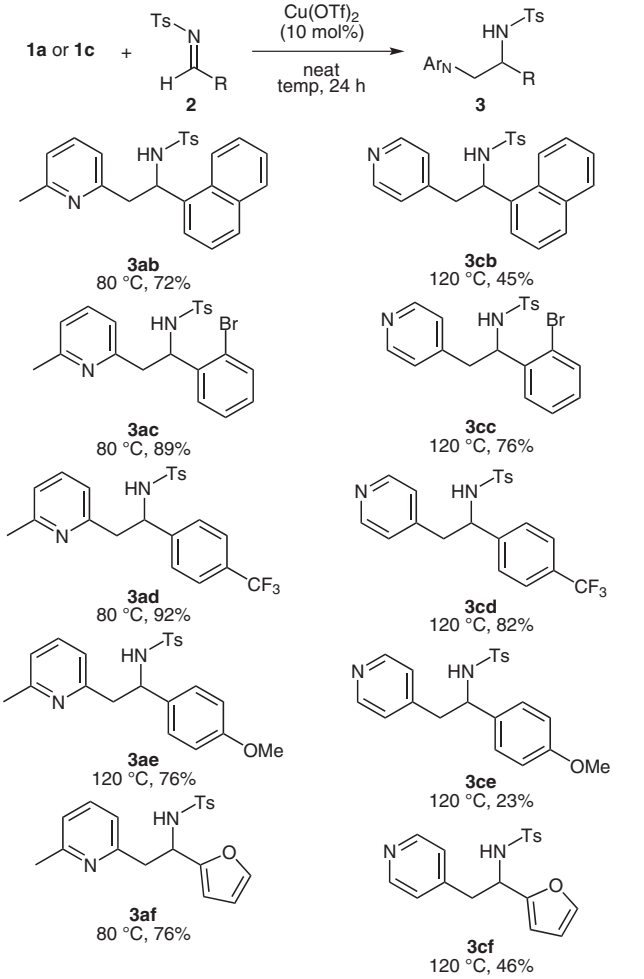


Scheme 2 Copper-catalyzed addition of azaarenes **1a**–**f** and benzoxazole **1j** to imine **2a**. *Reagents and conditions*: **1** (10 equiv), imine **2a** (0.25 mmol), $Cu(OTf)_3$ (10 mol%), solvent-free conditions, 60, 80 or 120 °C. Isolated yield after purification by silica gel column chromatography is shown for each run.

On the other hand, the reactivity of 4-picoline (**1c**) was strongly dependent on the reactivity of the imine. Good yield was obtained for aryl imines with an electron-withdrawing substituent, but poor to moderate results were observed for less reactive imines (Scheme 3). Although there remains room for improvement in the reactivity with 4-picoline (**1c**), the results with **1c** are still noteworthy because previously reported Lewis acid catalyzed conditions were not applicable to this substrate.[4a,b] On the other hand, attempts to use enolizable aliphatic imines failed, possibly due to undesirable isomerization of imines to enamides.

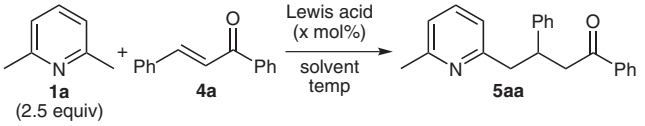
In previous reports, Lewis acid catalyzed 1,2-addition reactions to imines and activated carbonyl compounds have been achieved.[4] In contrast, the 1,4-addition to electron-deficient alkenes under catalytic conditions has not been investigated.[16] Thus, we tried to expand the electrophile scope to enones; to this end, lutidine **1a** and enone **4a** were selected as model substrates.

To our surprise, the reactivity of enones toward azaarenes was much lower than imines, and $Cu(OTf)_2$, which was the best catalyst for imines, did not afford the product (Table 2, entry 1). Because solvent-free conditions with excess lutidine (**1a**) were not suitable for the 1,4-addition reaction, reoptimization of the reaction was performed in



Scheme 3 Copper-catalyzed addition of lutidine (**1a**) and 4-picoline (**1c**) to imines **2**: *Reagents and conditions*: **1** (10 equiv), imine **2** (0.25 mmol), $Cu(OTf)_3$ (10 mol%), solvent-free conditions, 80 or 120 °C. Isolated yield after purification by silica gel column chromatography is shown for each run.

Table 2 Optimization Studies for the Addition to Chalcone



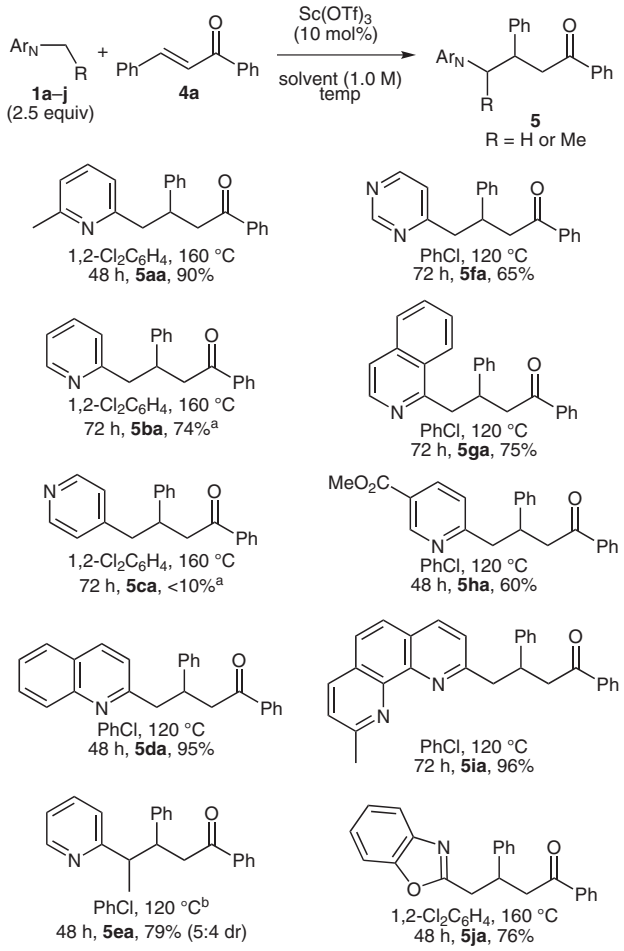
Entry	Lewis acid (x mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$Cu(OTf)_2$ (20)	PhCl	120	14	0
2	$Al(OTf)_3$ (20)	PhCl	120	14	0
3	$In(OTf)_3$ (20)	PhCl	120	14	0
4	$Fe(OTf)_3$ (20)	PhCl	120	14	0
5	$Mg(OTf)_2$ (20)	PhCl	120	14	0
6	$Zn(OTf)_2$ (20)	PhCl	120	14	0
7	$Bi(OTf)_3$ (20)	PhCl	120	14	0
8	$Sc(OTf)_3$ (20)	PhCl	120	14	71
9	$Y(OTf)_3$ (20)	PhCl	120	14	71
10	$Gd(OTf)_3$ (20)	PhCl	120	14	33
11	$Sm(OTf)_3$ (20)	PhCl	120	14	0
12	$La(OTf)_3$ (20)	PhCl	120	14	trace
13	$ScBr_3$ (20)	PhCl	120	14	51
14	$ScCl_3$ (20)	PhCl	120	14	30
15	$Sc(OTf)_3$ (10)	PhCl	120	48	73[b]
16	$Sc(OTf)_3$ (10)	PhCl	120	72	90[b]
17	$Sc(OTf)_3$ (10)	1,2-Cl_2-C_6H_4	160	48	90[b]

[a] Determined by ^1H NMR analysis.
[b] Isolated yield after purification by column chromatography.

chlorobenzene. Rescreening of other Lewis acids revealed that $Al(OTf)_3$, $In(OTf)_3$, $Fe(OTf)_3$, $Mg(OTf)_2$, $Zn(OTf)_2$, and $Bi(OTf)_3$, which were also useful for the addition to imines, did not promote the desired reaction at all (Table 2, entries 2–7). On the other hand, the results using rare-earth metal triflates [$RE(OTf)_3$] were promising (Table 2, entries 8–12). The reactivity changed in correlation with the Lewis acidity of rare earth metal triflates (Sc, Y > Gd > Sm, La) reported by Imamoto and co-workers,[17] and 20 mol% $Sc(OTf)_3$ and $Y(OTf)_3$ gave the best reactivity (71% yield in both cases; Table 2, entries 8 and 9). The differing ability of Lewis acids to effect 1,2-addition and 1,4-addition implied that the activation of electrophiles by Lewis acid in the presence of stoichiometric amounts of Lewis basic azaarenes **1** would be a key to efficient promotion of the 1,4-addition reaction. $ScBr_3$ and $ScCl_3$ were also examined, but the yield was not satisfactory (Table 2, entries 13 and 14). The reaction proceeded in good yield with 10 mol% $Sc(OTf)_3$, although a longer reaction time was required at 120 °C (72 h, 90% isolated yield; Table 2, entry 16). At 160 °C, the reaction was complete after 48 hours using 10 mol% $Sc(OTf)_3$ (90% isolated yield; Table 2, entry 17).

The substrate scope and limitations of donors is summarized in Scheme 4. Benzylic $C(sp^3)$-H of alkyl-substituted pyridines, quinoline, isoquinoline, pyrimidine, phenanthroline, and benzoxazole were investigated. 2-Picoline (**1b**) was less reactive than **1a**, and 20 mol% $Sc(OTf)_3$ at 160 °C was required to obtain **5ba** in 74% yield. In contrast to the 1,2-addition to imines (Scheme 2 and Scheme 3), use of 4-picoline (**1c**) resulted in poor yield even at high temperature and using high catalyst loading. Attempts to improve the yield with **1c** as the donor was not successful in 1,4-addition. 2-Ethylpyridine (**1e**) reacted smoothly and selectively at the benzylic position. The use of 10 mol% $Y(OTf)_3$ at 120 °C was optimal for 2-ethylpyridine (**1e**), and the product **5ea** was obtained in 79% yield after 48 hours; the diastereoselectivity was, however, poor (5:4 dr). Other azaarenes, such as quinoline, pyrimidine, isoquinoline, and phenanthroline showed good reactivity with 10 mol% $Sc(OTf)_3$ at 120 °C, giving products **5da**, **5fa**, **5ga**, and **5ia** in 65–96% yield. Methyl-sub-

stituted pyridine **1h**, bearing an ester functional group, was compatible under the reaction conditions, and **5ha** was obtained in 60% yield. 2-Methylbenzoxazole (**1j**) was also applicable, giving product **5ja** in 76% yield.



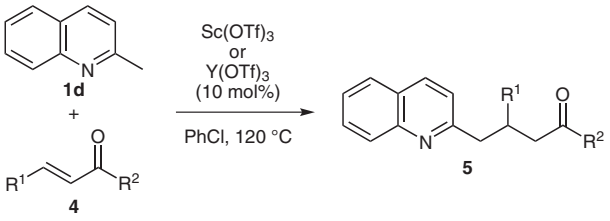
Scheme 4 Scandium-catalyzed addition of azaarenes **1** to chalcone **4a**: *Reagents and conditions*: **1** (2.5 equiv), chalcone **4a** (0.25 mmol), $Sc(OTf)_3$ (10 mol%), solvent (1.0 M), 120–160 °C unless otherwise noted. Isolated yield after purification by silica gel column chromatography is shown for each run. [a] 20 mol% of $Sc(OTf)_3$ was used. [b] 10 mol% of $Y(OTf)_3$ was used instead of $Sc(OTf)_3$.

The substrate scope of acceptors is summarized in Table 3. The reactions of chalcone derivatives **4b–e** with either an electron-withdrawing group or an electron-donating group proceeded in good yield (79–91%). Heteroaryl-substituted enones **4f–h** were also applicable, giving the products in 72–93% yield. With dienone **4i**, 1,4-addition predominated over 1,6-addition, and the 1,4-adduct **5di** was obtained in 78% yield.

Although the 1,4-addition to chalcone derivatives proceeded smoothly, less reactive alkenes, such as alkyl substituted enones and α,β-unsaturated esters, did not afford the desired products. To compensate the limited generality of electrophiles, we investigated the use of α,β-unsaturated *N*-acylpyrrole **4j** as an electrophile (Scheme 5). The reactivity of **4j** was similar to that of chalcone derivatives,[18,19] and the product **5dj** was obtained in 81% yield.

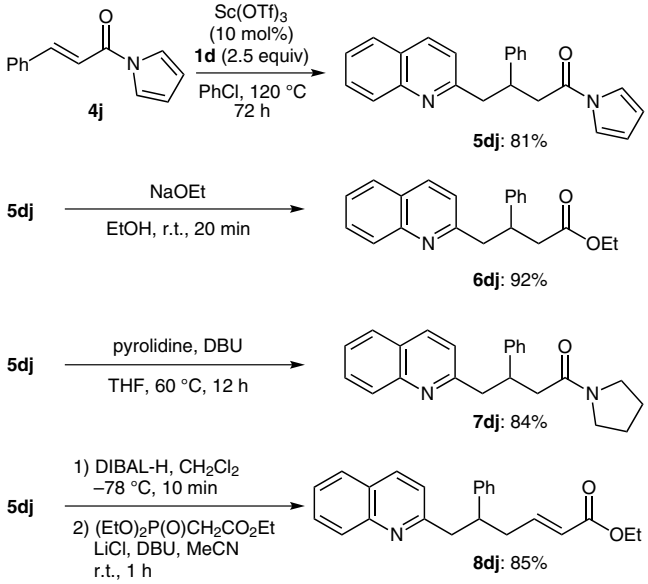
Because the *N*-acylpyrrole unit can be regarded as an ester surrogate, its synthetic utility was examined in a number of transformations.

Table 3 Scandium-Catalyzed Addition of Azaarene **1d** to Enones[a]



Entry	R^1	R^2	4	Cat.	Time (h)	5	Yield (%)[b]
1	Ph	4-FC_6H_4	**4b**	Y	36	**5db**	91
2	Ph	4-$MeOC_6H_4$	**4c**	Y	48	**5dc**	79
3	4-ClC_6H_4	Ph	**4d**	Sc	72	**5dd**	86
4	4-$MeOC_6H_4$	Ph	**4e**	Y	48	**5de**	81
5	Ph	2-thienyl	**4f**	Sc	72	**5df**	72
6	Ph	3-thienyl	**4g**	Sc	72	**5dg**	93
7	2-furyl	Ph	**4h**	Y	36	**5dh**	85
8[c]	(*E*)-PhCH=CH	Ph	**4i**	Y	48	**5di**	78

[a] Reaction conditions: **1d** (2.5 equiv), enone **4** (0.25 mmol), $Sc(OTf)_3$ or $Y(OTf)_3$ (10 mol%), solvent (1.0 M), 120 °C unless otherwise noted.
[b] Isolated yield after purification by silica gel column chromatography.
[c] 20 mol% of $Sc(OTf)_3$ was used.



Scheme 5 1,4-Addition of **1d** to α,β-unsaturated *N*-acylpyrrole **4j** and transformation of the *N*-acylpyrrole unit of **5dj**

The *N*-acylpyrrole unit was readily converted into an ethyl ester unit by treatment with sodium ethoxide at room tem-

perature for 20 minutes, giving **6dj** in 92% yield. Substitution with pyrrolidine also proceeded smoothly in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 60 °C for 12 hours (**7dj**; 84% yield). In addition to substitution reactions, the reduction of **5dj** with diisobutylaluminum hydride (DIBAL-H) gave pyrrole carbinols as diastereomeric mixtures. Under Masamune–Roush conditions,[20] α,β-unsaturated ethyl ester **8dj**, which can be regarded as 1,6-addition adduct of **1d**, was obtained in 85% yield (two steps) via generation of the aldehyde in situ from the crude pyrrole carbinols.

In summary, we have succeeded in the Lewis acid catalyzed functionalization of benzylic C(sp^3)-H in alkyl-substituted azaarenes under proton transfer conditions. The addition to *N*-Ts imines proceeded under solvent-free conditions using various Lewis acids. $Cu(OTf)_2$ was the best Lewis acid, and 1,2-addition of various azaarenes including 4-picoline proceeded at 60–120 °C, giving the desired products in 23–92% yield. On the other hand, strongly Lewis acidic rare earth metal triflates, $Sc(OTf)_3$ and $Y(OTf)_3$, were essential to promote the 1,4-addition of alkyl-substituted azaarenes to enones and an α,β-unsaturated *N*-acylpyrrole, and products were obtained in 60–96% yield. Transformation of the product from α,β-unsaturated *N*-acylpyrrole was also demonstrated.

Infrared (IR) spectra were recorded with a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded with JEOL JNM-LA500 and JNM-ECX500 spectrometers, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ are reported relative to $CHCl_3$ (δ = 7.26 ppm for ^{1}H NMR) and $CDCl_3$ (δ = 77.0 ppm for ^{13}C NMR) as an internal reference, respectively. ESI mass spectra were measured with a Waters ZQ4000 spectrometer (LRMS), and a JEOL JMS-T100LC AccuTOF spectrometer (HRMS). Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Reactions were carried out using flame-dried glassware in anhydrous solvents under an argon atmosphere.

Copper-Catalyzed Addition of 1 to 2; General Procedure A (Scheme 2 and Scheme 3)

To a flame-dried test tube was added $Cu(OTf)_2$ (0.025 mmol, 10 mol%) in a glove box. To the test tube were further added imine **2** (0.25 mmol) and azaarene **1** (2.5 mmol) at r.t. The mixture was stirred at 120, 80 or 60 °C for 24 h, and then diluted with EtOAc and quenched by passing through a short pad of silica gel. After evaporation of the solvent, the crude residue was purified by flash silica gel column chromatography (hexane–EtOAc, 4:1→1:1) to give **3**. Compounds **3aa**, **3ba**, **3da**, **3ab**, **3ac**, **3ad**, **3ae**, and **3af** are known.[3i,4a,b]

Scandium-Catalyzed Addition of 1 to 4a; General Procedure B (Scheme 4 and Table 3)

To a flame-dried test tube was added $Sc(OTf)_3$ or $Y(OTf)_3$ (0.025 mmol, 10 mol%) in a glove box. To the test tube were further added enone **4** (0.25 mmol), chlorobenzene or 1,2-dichlorobenzene (0.25 mL), and azaarene **1** (0.625 mmol), at r.t. The resulting mixture was stirred at 120 or 160 °C for the time indicated in Scheme 4 and Table 3, and then diluted with EtOAc and quenched by passing through a short pad of silica gel. After evaporation of the solvent, the crude residue was purified by flash silica gel column chromatography (hexane–EtOAc, 10:1→4:1) to give **5**.

4-Methyl-*N*-[1-phenyl-2-(pyridine-4-yl)ethyl]benzenesulfonamide (3ca)

Prepared according to General Procedure A.

Yield: 59.9 mg (68%); colorless liquid.

IR (neat): 3275, 3030, 2859, 1602, 1456, 1326, 1157, 1092, 811, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.98 (dd, *J* = 7.4, 13.8 Hz, 1 H), 3.06 (dd, *J* = 7.0, 13.8 Hz, 1 H), 4.52 (ddd, *J* = 7.0, 7.0, 7.4 Hz, 1 H), 6.78–6.88 (m, 2 H), 6.92–7.02 (m, 2 H), 7.06–7.19 (m, 4 H), 7.42–7.51 (m, 2 H), 8.20–8.40 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 43.2, 58.6, 124.6, 126.5, 126.9, 127.9, 128.6, 129.4, 137.1, 139.5, 143.3, 145.7, 149.6.

MS (ESI): *m*/*z* = 375 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{20}N_2NaO_2S^+$: 375.1143; found: 375.1139.

4-Methyl-*N*-[1-phenyl-2-(pyridine-2-yl)propyl]benzenesulfonamide (3ea)

Prepared according to General Procedure A.

Yield: 79.6 mg (87%); colorless solid; diastereomeric mixture (dr 2:1).

IR (KBr): 3276, 1560, 1436, 1326, 1160, 1093, 915, 813, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 1.18 (d, *J* = 7.4 Hz, 3 H), 2.25 (s, 3 H), 3.13–3.24 (m, 1 H), 4.46–4.55 (m, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.81–6.88 (m, 2 H), 6.96–7.08 (m, 5 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.37–7.45 (m, 3 H), 7.76–7.80 (m, 1 H), 8.45–8.50 (m, 1 H); δ (minor isomer) = 1.21 (d, *J* = 7.0 Hz, 3 H), 2.30 (s, 3 H), 3.04–3.14 (m, 1 H), 4.53–4.60 (m, 1 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 7.05–7.12 (m, 5 H), 7.34 (d, *J* = 6.4 Hz, 1 H), 7.44–7.50 (m, 3 H), 7.79–7.82 (m, 1 H), 8.49–8.54 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 21.3, 45.7, 62.1, 121.9, 122.4, 126.4, 126.8, 127.0, 127.6, 129.0, 136.6, 137.3.139.2, 142.5, 148.6, 161.7; δ (second isomer) = 19.1, 21.5, 46.8, 62.6, 121.9, 123.4, 126.4, 126.8, 127.4, 127.9, 129.0, 136.7, 138.9, 143.4, 148.7, 162.1.

LRMS (ESI): *m*/*z* = 389 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{22}N_2NaO_2S^+$: 389.1300; found: 389.1304.

4-Methyl-*N*-[1-phenyl-2-(pyrimidin-4-yl)ethyl]benzenesulfonamide (3fa)

Prepared according to General Procedure A.

Yield: 41.5 mg (47%); colorless solid; mp 106–107 °C.

IR (KBr): 3855, 3189, 2926, 2381, 1586, 1314, 1062, 964, 810, 705, 660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.97–3.09 (m, 2 H), 4.67–4.78 (m, 1 H), 6.43 (d, *J* = 6.4 Hz, 1 H), 6.85 (d, *J* = 4.9 Hz, 1 H), 6.98–7.15 (m, 8 H), 7.42–7.52 (m, 2 H), 8.34–8.53 (m, 1 H), 8.98 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 44.0, 57.0, 121.6, 126.4, 127.0, 127.6, 128.4, 129.3, 137.4, 140.0, 143.0, 157.1, 158.2, 165.9.

MS (ESI): *m*/*z* = 376 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}N_3NaO_2S^+$: 376.1096; found: 376.1092.

4-Methyl-*N*-[1-(naphthalene-1-yl)-2-(pyridine-4-yl)]benzenesulfonamide (3cb)

Prepared according to General Procedure A.

Yield: 45.2 mg (45%); colorless solid; mp 110–112 °C.

IR (KBr): 3855, 3271, 2923, 1604, 1422, 1327, 1158, 1079, 743, 669 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ = 2.10 (s, 3 H), 2.93 (dd, *J* = 8.5, 13.9 Hz, 1 H), 2.99 (dd, *J* = 6.1, 13.9 Hz, 1 H), 5.22 (ddd, *J* = 6.1, 8.0, 8.5 Hz, 1 H), 6.26 (d, *J* = 8.0 Hz, 1 H), 6.72–6.83 (m, 2 H), 6.86–6.96 (m, 2 H), 7.11–7.24 (m, 2 H), 7.20 (dd, *J* = 8.3, 8.3 Hz, 1 H), 7.27–7.40 (m, 3 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 7.68 (dd, *J* = 2.5, 5.8 Hz, 1 H), 7.84 (d, *J* = 7.0 Hz, 1 H), 8.05–8.20 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 43.1, 55.3, 123.4, 125.5, 125.7, 126.3, 126.7, 127.4, 127.5, 128.9, 130.0, 130.1, 131.2, 134.7, 137.8, 138.7, 144.0, 147.6, 150.5.

MS (ESI): *m*/*z* = 425 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{22}N_2NaO_2S^+$: 425.1300; found: 425.1301.

_N_-[1-(2-Bromophenyl)-2-(pyridine-4-yl)ethyl]-4-methylbenzenesulfonamide (3cc)
Prepared according to General Procedure A.

Yield: 81.7 mg (76%); colorless solid; mp 106–108 °C.

IR (KBr): 3855, 3651, 2402, 1603, 1420, 1328, 1157, 1092, 951, 661 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.77 (dd, *J* = 9.5, 14.1 Hz, 1 H), 3.03 (dd, *J* = 5.2, 14.1 Hz, 1 H), 4.91–5.06 (m, 1 H), 5.85 (d, *J* = 7.3 Hz, 1 H), 6.86–7.10 (m, 5 H), 7.13 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.21 (d, *J* = 7.4 Hz, 1 H), 7.45–7.50 (m, 3 H), 8.16–8.72 (br, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 41.8, 57.5, 122.3, 126.9, 127.8, 128.3, 129.1, 129.4, 132.9, 136.3, 139.2, 143.4, 145.4, 149.6.

MS (ESI): *m*/*z* 453 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}N_2NaO_2SBr^+$: 453.0248; found: 453.0240.

4-Methyl-_N_-{2-(pyridine-4-yl)-1-[4-(trifluoromethyl)phenyl]ethyl}benzenesulfonamide (3cd)
Prepared according to General Procedure A.

Yield: 86.1 mg (82%); colorless solid; mp 109–110 °C.

IR (KBr): 3855, 3736, 3066, 2852, 1606, 1421, 1325, 1160, 1067, 813, 661 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.94 (dd, *J* = 7.0, 14.1 Hz, 1 H), 3.02 (dd, *J* = 8.0, 14.1 Hz, 1 H), 4.62 (ddd, *J* = 7.0, 7.3, 8.0 Hz, 1 H), 5.79–5.96 (m, 1 H), 6.78–6.94 (m, 2 H), 6.97–7.16 (m, 4 H), 7.30–7.44 (m, 4 H), 8.30–8.40 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 42.8, 58.1, 124.6, 125.4 (q, $^3J_{C-F}$ = 3.9 Hz), 126.0 (q, $^1J_{C-F}$ = 272 Hz), 126.8, 127.0, 129.4, 129.9 (q, $^2J_{C-F}$ = 32.6 Hz), 136.8, 143.5, 143.6, 145.3, 149.6.

MS (ESI): *m*/*z* = 443 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{19}N_2NaO_2SF_3^+$: 443.1017; found: 443.1023.

_N_-[1-(4-Methoxyphenyl)-2-(pyridine-4-yl)ethyl]-4-methylbenzenesulfonamide (3ce)
Prepared according to General Procedure A.

Yield: 22.0 mg (23%); colorless solid; mp 138–140 °C.

IR (KBr): 3854, 3736, 3049, 1597, 1314, 1065, 971, 765, 705, 660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.95 (dd, *J* = 8.0, 13.5 Hz, 1 H), 3.06 (dd, *J* = 7.0, 13.5 Hz, 1 H), 3.71 (s, 3 H), 4.44 (ddd, *J* = 7.0, 7.1, 8.0 Hz, 1 H), 5.52 (d, *J* = 7.1 Hz, 1 H), 6.61–6.65 (m, 2 H), 6.78–6.92 (m, 4 H), 7.04–7.13 (m, 2 H), 7.42–7.51 (m, 2 H), 8.30–8.33 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 43.2, 55.2, 58.2, 113.9, 124.7, 126.9, 127.8, 129.4, 131.5, 137.3, 143.2, 146.0, 149.5, 159.1.

MS (ESI): *m*/*z* = 405 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{22}N_2NaO_2S^+$: 405.1249; found: 405.1240.

_N_-[1-(Furan-2-yl)-2-(pyridin-4-yl)ethyl]-4-methylbenzenesulfonamide (3cf)
Prepared according to General Procedure A.

Yield: 39.3 mg (46%); colorless solid; mp 115–118 °C.

IR (KBr): 3243, 2855, 1604, 1337, 1160, 1094, 846, 740, 660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 3.10 (dd, *J* = 7.3, 13.3 Hz, 1 H), 3.16 (dd, *J* = 5.8, 13.3 Hz, 1 H), 4.67–4.77 (m, 1 H), 5.83 (br s, 1 H), 5.93 (d, *J* = 8.9 Hz, 1 H), 6.14 (d, *J* = 1.3 Hz, 1 H), 6.77–6.92 (m, 2 H), 7.11–7.26 (m, 3 H), 7.55–7.64 (m, 2 H), 8.25–8.43 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 40.5, 52.2, 107.8, 110.3, 124.7, 126.8, 129.4, 137.5, 142.0, 143.2, 145.5, 149.4, 151.5.

MS (ESI): *m*/*z* = 365 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}N_2NaO_3S^+$: 365.0936; found: 365.0941.

4-(6-Methylpyridin-2-yl)-1,3-diphenylbutan-1-one (5aa)
Prepared according to General Procedure B.

Yield: 70.9 mg (90%); colorless solid; mp 86–87 °C.

IR (KBr): 3061, 2944, 1677, 1595, 1499, 1222, 760, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.48 (s, 3 H), 3.17 (d, *J* = 7.6 Hz, 2 H), 3.35 (dd, *J* = 5.8, 16.5 Hz, 1 H), 3.41 (dd, *J* = 7.5, 16.5 Hz, 1 H), 3.90–4.00 (m, 1 H), 6.87 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 7.13–7.20 (m, 1 H), 7.23–7.32 (m, 4 H), 7.38–7.46 (m, 3 H), 7.50–7.56 (m, 1 H), 7.84–7.90 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.4, 41.6, 44.3, 45.2, 120.5, 120.7, 126.4, 127.6, 128.1, 128.4, 128.4, 132.8, 136.4, 137.2, 144.3, 157.7, 159.2, 198.8.

MS (ESI): *m*/*z* = 338 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO^+$: 338.1521; found: 338.1515.

1,3-Diphenyl-4-(pyridin-2-yl)butan-1-one (5ba)
Prepared according to General Procedure B.

Yield: 55.7 mg (74%); colorless solid; mp 89–90 °C.

IR (KBr): 3028, 2926, 1677, 1472, 1449, 1260, 985, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.08 (dd, *J* = 7.3, 13.2 Hz, 1 H), 3.15 (dd, *J* = 7.9, 13.2 Hz, 1 H), 3.25–3.36 (m, 2 H), 3.81–3.90 (m, 1 H), 6.95–7.02 (m, 2 H), 7.05–7.09 (m, 1 H), 7.13–7.20 (m, 4 H), 7.29–7.37 (m, 2 H), 7.40–7.48 (m, 2 H), 7.75–7.81 (m, 2 H), 8.38–8.44 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.7, 44.4, 45.1, 121.2, 123.6, 126.4, 127.6, 128.0, 128.4, 128.4, 132.8, 136.1, 137.2, 144.0, 149.2, 159.9, 198.6.

MS (ESI): *m*/*z* = 324 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{19}NNaO^+$: 324.1364; found: 324.1372.

1,3-Diphenyl-4-(quinolin-2-yl)butan-1-one (5da)
Prepared according to General Procedure B.

Yield: 83.4 mg (95%); colorless solid; mp 94–95 °C.

IR (KBr): 3061, 2943, 1677, 1595, 1507, 1416, 1224, 1076, 748, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.32–3.51 (m, 4 H), 4.04–4.13 (m, 1 H), 7.14–7.20 (m, 1 H), 7.21–7.32 (m, 5 H), 7.34–7.41 (m, 2 H), 7.44–7.52 (m, 2 H), 7.62–7.69 (m, 1 H), 7.74 (d, *J* = 8.3 Hz, 1 H), 7.81–7.87 (m, 2 H), 7.95–8.02 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 44.4, 45.8, 121.9, 125.8, 126.5, 126.8, 127.5, 127.6, 128.1, 128.4, 128.5, 128.9, 129.3, 132.8, 136.1, 137.1, 144.1, 147.8, 160.4, 198.7.

MS (ESI): *m*/*z* = 374 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{21}NNaO^+$: 374.1521; found: 374.1527.

1,3-Diphenyl-4-(pyridin-2-yl)pentan-1-one (5ea)
Prepared according to General Procedure B as a 5:4 diastereomeric mixture. Attempts to isolate each diastereoisomer resulted in failure.

Yield: 62.2 mg (79%); colorless oil.

IR (neat): 3039, 2962, 1677, 1593, 1449, 1260, 749, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 1.40 (d, *J* = 7.0 Hz, 3 H), 3.29–3.36 (m, 1 H), 3.42 (dd, *J* = 9.0, 16.3 Hz, 1 H), 3.54 (dd, *J* = 4.9, 16.3 Hz, 1 H), 3.81–3.87 (m, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.99–7.19 (m, 4 H), 7.27–7.47 (m, 5 H), 7.49–7.53 (m, 1 H), 7.83–7.87 (m, 2 H), 8.47 (d, *J* = 4.3 Hz, 1 H); δ (minor isomer) = 1.08 (d, *J* = 7.0 Hz, 3 H), 2.99 (dd, *J* = 3.7, 16.2 Hz, 1 H), 3.20–3.29 (m, 2 H), 3.68–3.75 (m, 1 H), 6.99–7.14 (m, 5 H), 7.27–7.47 (m, 5 H), 7.61–7.66 (m, 1 H), 7.67–7.71 (m, 2 H), 8.58 (d, *J* = 4.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 41.3, 46.6, 47.6, 121.1, 122.7, 126.1, 127.9, 128.0, 128.3, 128.4, 132.7, 136.6, 137.3, 142.8, 148.8, 164.1, 199.1; δ (second isomer) = 19.8, 44.0, 47.1, 47.8, 121.6, 122.4, 126.5, 128.0, 128.3, 128.3, 128.4, 132.6, 135.8, 137.1, 143.1, 149.3, 165.0, 198.9.

MS (ESI): *m*/*z* = 316 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}NO^+$: 316.1701; found: 316.1700.

1,3-Diphenyl-4-(pyrimidin-4-yl)butan-1-one (5fa)
Prepared according to General Procedure B.

Yield: 49.1 mg (65%); colorless solid; mp 92–93 °C.

IR (KBr): 3033, 2929, 1676, 1580, 1470, 1380, 1075, 740, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.10 (dd, *J* = 8.5, 13.6 Hz, 1 H), 3.25 (dd, *J* = 6.5, 13.6 Hz, 1 H), 3.41 (d, *J* = 6.7 Hz, 2 H), 3.92–3.99 (m, 1 H), 7.00 (d, *J* = 6.2 Hz, 1 H), 7.14–7.26 (m, 5 H), 7.41–7.45 (m, 2 H), 7.52–7.56 (m, 1 H), 7.83–7.89 (m, 2 H), 8.49 (d, *J* = 5.1 Hz, 1 H), 9.06 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.7, 44.2, 44.6, 121.3, 126.8, 127.5, 128.0, 128.6, 128.6, 133.1, 137.0, 143.1, 156.5, 158.6, 168.4, 198.2.

MS (ESI): *m*/*z* = 325 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{18}N_2NaO^+$: 325.1317; found: 325.1309.

4-(Isoquinolin-1-yl)-1,3-diphenylbutan-1-one (5ga)
Prepared according to General Procedure B.

Yield: 65.8 mg (75%); colorless solid; mp 84–85 °C.

IR (KBr): 2942, 1678, 1597, 1501, 1379, 1259, 1178, 1032, 903, 821, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.44 (dd, *J* = 7.3, 17.0 Hz, 1 H), 3.50 (dd, *J* = 6.1, 17.0 Hz, 1 H), 3.62–3.73 (m, 2 H), 4.06–4.15 (m, 1 H), 7.11–7.17 (m, 1 H), 7.19–7.32 (m, 4 H), 7.34–7.42 (m, 2 H), 7.44–7.50 (m, 2 H), 7.57–7.70 (m, 2 H), 7.77 (d, *J* = 7.9 Hz, 1 H), 7.82–7.88 (m, 2 H), 8.26 (d, *J* = 8.3 Hz, 1 H), 8.32 (d, *J* = 5.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.2, 42.4, 44.5, 119.6, 125.4, 126.5, 127.2, 127.4, 127.5, 128.0, 128.4, 128.5, 129.9, 132.8, 136.3, 137.1, 141.6, 144.5, 159.8, 198.8.

MS (ESI): *m*/*z* = 374 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{21}NNaO^+$: 374.1521; found: 374.1529.

Methyl 6-(4-oxo-2,4-diphenylbutyl)nicotinate (5ha)
Prepared according to General Procedure B.

Yield: 52.1 mg (60%); colorless solid; mp 89–90 °C.

IR (KBr): 3026, 2926, 1720, 1677, 1594, 1449, 1380, 1354, 1260, 1076, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19 (dd, *J* = 7.9, 13.4 Hz, 1 H), 3.32 (dd, *J* = 7.3, 13.4 Hz, 1 H), 3.36–3.44 (m, 2 H), 3.91 (s, 3 H), 3.92–3.98 (m, 1 H), 7.04–7.09 (m, 1 H), 7.13–7.34 (m, 5 H), 7.37–7.45 (m, 2 H), 7.50–7.56 (m, 1 H), 7.84–7.90 (m, 2 H), 8.08 (dd, *J* = 1.9, 8.0 Hz, 1 H), 9.07 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 44.5, 45.0, 52.2, 123.3, 123.7, 126.6, 127.5, 128.0, 128.5, 128.5, 133.0, 137.1, 143.5, 150.4, 164.5, 165.9, 198.4.

MS (ESI): *m*/*z* = 382 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{21}NNaO_3^+$: 382.1419; found: 382.1414.

4-(9-Methyl-1,10-phenanthrolin-2-yl)-1,3-diphenylbutan-1-one (5ia)
Prepared according to General Procedure B.

Yield: 99.9 mg (96%); colorless solid; mp 151–152 °C.

IR (KBr): 3051, 1678, 1449, 1380, 1260, 1075, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.93 (s, 3 H), 3.49 (dd, *J* = 8.6, 16.8 Hz, 1 H), 3.57 (dd, *J* = 6.4, 14.1 Hz, 1 H), 3.66–3.74 (m, 2 H), 4.12–4.22 (m, 1 H), 7.13–7.18 (m, 1 H) 7.23–7.31 (m, 4 H), 7.33–7.40 (m, 3 H), 7.41–7.44 (m, 1 H), 7.45–7.50 (m, 1 H), 7.66 (d, *J* = 8.9 Hz, 1 H), 7.69 (d, *J* = 8.9 Hz, 1 H), 7.81–7.86 (m, 2 H), 8.05 (d, *J* = 8.2 Hz, 1 H), 8.10 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 41.2, 44.6, 45.7, 123.1, 123.4, 125.4, 125.6, 126.4, 126.8, 127.2, 127.8, 128.1, 128.2, 128.4, 132.5, 136.1, 136.2, 137.2, 144.5, 145.4, 145.5, 159.1, 160.5, 199.0.

MS (ESI): *m*/*z* = 439 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{24}N_2NaO^+$: 439.1786; found: 439.1789.

4-(Benzo[*d*]oxazol-2-yl)-1,3-diphenylbutan-1-one (5ja)
Prepared according to General Procedure B.

Yield: 64.8 mg (76%); yellow solid; mp 107–108 °C.

IR (KBr): 2926, 1678, 1594, 1541, 1437, 1260, 1075, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.25 (dd, *J* = 7.0, 15.0 Hz, 1 H), 3.32 (dd, *J* = 7.9, 15.0 Hz, 1 H), 3.37–3.44 (m, 2 H), 4.01–4.09 (m, 1 H), 7.07–7.13 (m, 1 H), 7.15–7.27 (m, 6 H), 7.31–7.39 (m, 3 H), 7.42–7.48 (m, 1 H), 7.50–7.56 (m, 1 H), 7.76–7.83 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.4, 39.1, 44.3, 110.4, 119.7, 124.1, 124.6, 126.9, 127.3, 128.0, 128.5, 128.7, 133.1, 136.9, 141.2, 143.0, 150.8, 165.0, 197.9.

MS (ESI): *m*/*z* = 364 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{19}NNaO_2^+$: 364.1313; found: 364.1324.

1-(4-Fluorophenyl)-3-phenyl-4-(quinolin-2-yl)butan-1-one (5db)
Prepared according to General Procedure B.

Yield: 84.1 mg (91%); colorless solid; mp 89–90 °C.

IR (KBr): 3028, 2926, 1678, 1594, 1449, 1355, 1260, 985, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.29–3.44 (m, 3 H), 3.45 (dd, *J* = 5.5, 11.0 Hz, 1 H), 4.04–4.13 (m, 1 H), 6.99–7.07 (m, 2 H), 7.13–

7.35 (m, 6 H), 7.46–7.52 (m, 1 H), 7.63–7.69 (m, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H), 7.82–7.92 (m, 2 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 8.00 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.1, 44.2, 45.8, 115.4 (d, $^2J_{C–F}$ = 21.7 Hz), 121.9, 125.9, 126.5, 126.7, 127.5, 127.6, 128.5, 128.8, 129.3, 130.7 (d, $^3J_{C–F}$ = 9.3 Hz), 133.5, 136.2, 144.0, 147.8, 160.3, 165.5 (d, $^1J_{C–F}$ = 254 Hz), 197.1.

MS (ESI): *m*/*z* = 392 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{20}FNNaO^+$: 392.1427; found: 392.1432.

1-(4-Methoxyphenyl)-3-phenyl-4-(quinolin-2-yl)butan-1-one (5dc)
Prepared according to General Procedure B.

Yield: 75.3 mg (79%); colorless solid; mp 109–110 °C.

IR (KBr): 3060, 2942, 1678, 1597, 1502, 1416, 1258, 1226, 821, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.28–3.43 (m, 4 H), 3.83 (s, 3 H), 4.01–4.10 (m, 1 H), 6.77–6.81 (m, 2 H), 7.09–7.15 (m, 1 H), 7.17–7.34 (m, 5 H), 7.42–7.50 (m, 1 H), 7.63–7.69 (m, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.78–7.85 (m, 2 H), 7.91–8.03 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.6, 44.0, 45.8, 55.4, 113.5, 121.9, 125.8, 126.4, 126.8, 127.5, 127.6, 128.4, 128.9, 129.2, 130.2, 130.3, 136.1, 144.2, 147.8, 160.5, 163.3, 197.2.

MS (ESI): *m*/*z* = 404 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{23}NNaO_2^+$: 404.1626; found: 404.1629.

3-(4-Chlorophenyl)-1-phenyl-4-(quinolin-2-yl)butan-1-one (5dd)
Prepared according to General Procedure B.

Yield: 82.8 mg (86%); colorless solid; mp 118–119 °C.

IR (KBr): 3060, 2941, 1678, 1597, 1502, 1416, 1258, 1226, 1075, 821, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.28–3.42 (m, 3 H), 3.47 (dd, *J* = 5.5, 16.8 Hz, 1 H), 4.04–4.12 (m, 1 H), 7.16–7.24 (m, 5 H), 7.35–7.42 (m, 2 H), 7.45–7.53 (m, 2 H), 7.64–7.69 (m, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H), 7.82–7.88 (m, 2 H), 7.98 (d, *J* = 8.6 Hz, 1 H), 8.01 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.8, 44.2, 45.6, 121.8, 126.0, 126.8, 127.5, 128.0, 128.5, 128.6, 128.9, 129.0, 129.4, 132.1, 133.0, 136.2, 137.0, 142.6, 147.8, 159.9, 198.4.

MS (ESI): *m*/*z* = 408 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{20}ClNNaO^+$: 408.1126; found: 408.1131.

3-(4-Methoxyphenyl)-1-phenyl-4-(quinolin-2-yl)butan-1-one (5de)
Prepared according to General Procedure B.

Yield: 77.1 mg (81%); colorless solid; mp 110–111 °C.

IR (KBr): 3060, 2940, 1678, 1597, 1502, 1416, 1226, 1075, 821, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35–3.46 (m, 3 H), 3.48 (dd, *J* = 5.5, 11.0 Hz, 1 H), 3.79 (s, 3 H), 4.05–4.12 (m, 1 H), 6.81–6.85 (m, 2 H), 7.22–7.27 (m, 3 H), 7.38–7.46 (m, 2 H), 7.49–7.58 (m, 2 H), 7.67–7.76 (m, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.86–7.92 (m, 2 H), 8.02–8.07 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.7, 44.6, 46.0, 55.1, 113.8, 121.9, 125.8, 126.8, 127.5, 128.0, 128.4, 128.5, 128.9, 129.3, 132.8, 136.1, 137.1, 147.8, 158.1, 160.5, 198.9.

MS (ESI): *m*/*z* = 404 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{23}NNaO_2^+$: 404.1626; found: 404.1630.

3-Phenyl-4-(quinolin-2-yl)-1-(thiophen-2-yl)butan-1-one (5df)
Prepared according to General Procedure B.

Yield: 64.3 mg (72%); colorless solid; mp 99–100 °C.

IR (KBr): 3053, 2922, 1677, 1595, 1449, 1262, 985, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.28–3.45 (m, 4 H), 4.03–4.12 (m, 1 H), 7.03–7.08 (m, 1 H), 7.12–7.18 (m, 1 H), 7.19–7.35 (m, 5 H), 7.46–7.52 (m, 1 H), 7.53 (d, *J* = 4.9 Hz, 1 H), 7.63–7.72 (m, 2 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.96–8.05 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.7, 45.1, 45.6, 121.9, 125.9, 126.6, 126.8, 127.5, 127.6, 127.9, 128.5, 128.9, 129.3, 131.9, 133.4, 136.2, 143.8, 144.6, 160.3, 191.5.

MS (ESI): *m*/*z* = 380 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{19}NNaOS^+$: 380.1085; found: 380.1096.

3-Phenyl-4-(quinolin-2-yl)-1-(thiophen-3-yl)butan-1-one (5dg)
Prepared according to General Procedure B.

Yield: 83.0 mg (93%); colorless solid; mp 92–93 °C.

IR (neat): 3060, 2927, 1676, 1595, 1504, 1415, 1225, 1076, 748, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.24 (dd, *J* = 8.1, 16.2 Hz, 1 H), 3.30–3.45 (m, 3 H), 4.00–4.07 (m, 1 H), 7.10–7.12 (m, 1 H), 7.15–7.30 (m, 6 H), 7.38 (d, *J* = 5.2 Hz, 1 H), 7.41–7.47 (m, 1 H), 7.62 (dd, *J* = 8.3, 8.3 Hz, 1 H), 7.70 (d, *J* = 8.3 Hz, 1 H), 7.93–8.02 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 45.6, 45.7, 121.9, 125.8, 126.0, 126.5, 126.8, 126.9, 127.5, 127.6, 128.5, 128.9, 129.3, 131.9, 136.1, 142.4, 144.0, 147.8, 160.3, 193.0.

MS (ESI): *m*/*z* = 380 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{19}NNaOS^+$: 380.1085; found: 380.1092.

3-(Furan-2-yl)-1-phenyl-4-(quinolin-2-yl)butan-1-one (5dh)
Prepared according to General Procedure B.

Yield: 72.5 mg (85%); yellow solid; mp 95–96 °C.

IR (KBr): 3061, 2926, 1678, 1595, 1448, 1260, 1076, 759, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.25–3.44 (m, 4 H), 4.07–4.16 (m, 1 H), 5.89 (br s, 1 H), 6.11 (br s, 1 H), 7.10–7.15 (m, 1 H), 7.21 (br s, 1 H), 7.30–7.36 (m, 2 H), 7.37–7.47 (m, 2 H), 7.53–7.64 (m, 1 H), 7.69 (d, *J* = 7.7 Hz, 1 H), 7.77–7.85 (m, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.0, 41.8, 43.1, 105.7, 110.1, 121.8, 125.9, 126.8, 127.5, 128.1, 128.5, 129.0, 129.3, 132.9, 136.1, 137.0, 141.1, 147.8, 156.7, 160.0, 198.4.

MS (ESI): *m*/*z* = 364 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{19}NNaO_2^+$: 364.1313; found: 364.1324.

(*E*)-1,5-Diphenyl-3-(quinolin-2-ylmethyl)pent-4-en-1-one (5di)
Prepared according to General Procedure B.

Yield: 73.6 mg (78%); yellow solid; mp 106–107 °C.

IR (KBr): 3060, 2927, 1678, 1593, 1449, 1260, 1075, 749, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.15 (dd, *J* = 7.6, 16.2 Hz, 1 H), 3.20–3.31 (m, 3 H), 3.62–3.71 (m, 1 H), 6.27 (dd, *J* = 7.9, 15.9 Hz, 1 H), 6.39 (d, *J* = 15.9 Hz, 1 H), 7.17–7.20 (m, 1 H), 7.21–7.27 (m, 4 H), 7.36–7.45 (m, 3 H), 7.46–7.55 (m, 2 H), 7.63–7.72 (m, 1 H),

7.77 (d, *J* = 8.3 Hz, 1 H), 7.88–7.94 (m, 2 H), 8.01 (d, *J* = 7.9 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.1, 43.3, 44.2, 122.1, 125.9, 126.2, 126.8, 127.1, 127.5, 128.1, 128.4, 128.5, 128.9, 129.3, 130.4, 132.5, 132.9, 136.2, 137.2, 137.3, 160.4, 160.4, 199.0.

MS (ESI): *m*/*z* = 400 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{23}NNaO^+$: 400.1677; found: 400.1684.

3-Phenyl-1-(1*H*-pyrrol-1-yl)-4-(quinolin-2-yl)butan-1-one (5dj)
Prepared according to General Procedure B.

Yield: 69.0 mg (81%); yellow solid; mp 84–85 °C.

IR (KBr): 3050, 2925, 1715, 1596, 1470, 1355, 1267, 1075, 739, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.20 (dd, *J* = 8.6, 16.2 Hz, 1 H), 3.33–3.46 (m, 3 H), 4.03–4.11 (m, 1 H), 6.19–6.25 (m, 2 H), 7.15–7.24 (m, 2 H), 7.25–7.35 (m, 6 H), 7.45–7.53 (m, 1 H), 7.65–7.71 (m, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H), 7.98–8.04 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.3, 41.6, 45.4, 112.9, 119.0, 121.8, 126.0, 126.8, 127.5, 127.5, 128.6, 128.9, 129.4, 136.3, 143.3, 147.8, 159.9, 169.0.

MS (ESI): *m*/*z* = 363 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}N_2NaO^+$: 363.1473; found: 363.1481.

Ethyl 3-Phenyl-4-(quinolin-2-yl)butanoate (6dj)
To a solution of **5dj** (16.8 mg, 49.4 μmol) in EtOH (0.30 mL) was added NaOEt (6.7 mg, 98 μmol) at 0 °C. After stirred for 20 min at r.t., the reaction was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash silica gel column chromatography (hexane–Et_2O, 3:1) to afford **6dj**.

Yield: 14.5 mg (92%); yellow oil.

IR (neat): 3064, 2981, 2929, 1731, 1599, 1503, 1262, 1179, 1031, 755, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.3 Hz, 3 H), 2.74 (dd, *J* = 8.8, 15.3 Hz, 1 H), 2.80 (dd, *J* = 6.1, 15.3 Hz, 1 H), 3.28–3.38 (m, 2 H), 3.78–3.87 (m, 1 H), 3.94 (q, *J* = 7.3 Hz, 2 H), 7.14 (d, *J* = 8.6 Hz, 1 H), 7.16–7.22 (m, 1 H), 7.24–7.29 (m, 4 H), 7.48–7.53 (m, 1 H), 7.68–7.73 (m, 1 H), 7.76 (d, *J* = 8.3 Hz, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 8.06 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 40.8, 42.6, 46.0, 60.4, 122.1, 126.1, 126.8, 127.0, 127.7, 127.8, 128.6, 129.2, 129.6, 136.3, 143.6, 148.2, 160.4, 172.3.

MS (ESI): *m*/*z* = 320 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_2^+$: 320.1651; found: 320.1652.

3-Phenyl-1-(pyrrolidin-1-yl)-4-(quinolin-2-yl)butan-1-one (7dj)
To a solution of **5dj** (20.6 mg, 60.5 μmol) in THF (0.20 mL) were added pyrrolidine (25 μL, 300 μmol) and DBU (45 μL, 300 μmol). The reaction mixture was warmed to 60 °C and stirred for 12 h. After cooling to r.t., the reaction was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash silica gel column chromatography (hexane–EtOAc, 1:1; then EtOAc–MeOH, 20:1) to afford **7dj**.

Yield: 17.6 mg (84%); yellow oil.

IR (neat): 3055, 2969, 2871, 1635, 1503, 1427, 1192, 1116, 829, 756, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57–1.81 (m, 4 H), 2.62 (dd, *J* = 7.3, 15.0 Hz, 1 H), 2.71 (dd, *J* = 6.4, 15.0 Hz, 1 H), 3.10–3.33 (m, 4 H), 3.35 (dd, *J* = 7.3, 13.7 Hz, 1 H), 3.42 (dd, *J* = 8.2, 13.7 Hz, 1 H), 3.92–4.01 (m, 1 H), 7.13–7.19 (m, 1 H), 7.22–7.28 (m, 2 H), 7.28–7.33 (m, 3 H), 7.44–7.51 (m, 1 H), 7.63–7.67 (m, 1 H), 7.74 (d, *J* = 7.1 Hz, 1 H), 7.98–8.04 (m, 2 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 24.1, 25.9, 40.8, 42.0, 45.2, 45.4, 46.5, 121.9, 125.7, 126.4, 126.8, 127.5, 127.6, 128.3, 128.7, 129.2, 136.0, 144.2, 147.6, 160.6, 169.7.

MS (ESI): *m*/*z* = 345 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O^+$: 345.1967; found: 345.1969.

(*E*)-Ethyl 5-Phenyl-6-(quinolin-2-yl)hex-2-enoate (8dj)
To a solution of **5dj** (31.7 mg, 93.1 μmol) in CH_2Cl_2 (1.0 mL) at 78 °C was added DIBAL-H (1.0 M in hexane, 0.28 mL, 280 μmol). After stirring for 10 min at 78 °C, the reaction was quenched with sat. aq NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation, the crude pyrrole carbinols (mixture of diastereomers) were used in the next step without further purification. To a suspension of flame-dried LiCl (12.3 mg, 290 μmol) in MeCN (0.20 mL) in a test tube were added ethyl diethylphosphonoacetate (56 μL, 280 μmol) and DBU (70 μL, 470 μmol) at r.t. The mixture was stirred at r.t. for 10 min to afford HWE reagent solution. To a solution of the crude pyrrole carbinols in MeCN (0.050 mL) was added HWE reagent solution in MeCN by using a syringe, using additional MeCN (0.10 mL) for rinsing. After stirring for 1 h at r.t., the reaction was quenched with sat. aq NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash silica gel column chromatography (hexane–Et_2O, 4:1→3:1) to give **8dj**.

Yield: 27.3 mg (85%); yellow oil.

IR (neat): 3060, 2981, 2927, 1716, 1654, 1599, 1504, 1267, 1205, 1040, 826, 756, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3 H), 2.59–2.70 (m, 2 H), 3.25 (dd, *J* = 8.0, 13.6 Hz, 1 H), 3.33 (dd, *J* = 7.1, 13.6 Hz, 1 H), 3.43–3.51 (m, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 5.73 (d, *J* = 15.6 Hz, 1 H), 6.81 (ddd, *J* = 7.3, 7.3, 15.6 Hz, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.13–7.19 (m, 3 H), 7.22–7.27 (m, 2 H), 7.45–7.51 (m, 1 H), 7.65–7.71 (m, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 8.04 (*J* = 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 25.9, 40.8, 42.0, 45.2, 45.4, 46.5, 121.9, 125.7, 126.4, 126.8, 127.5, 127.6, 128.3, 129.2, 136.0, 144.2, 147.6, 160.6, 169.7.

MS (ESI): *m*/*z* = 346 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}NO_2^+$: 346.1807; found: 346.1806.

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