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# Remote C–H bond functionalization reveals the distance-dependent isotope effect

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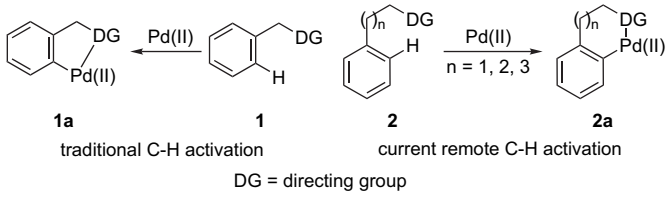
ABSTRACT

Iodination of remote aryl C–H bonds has been achieved using palladium acetate as the catalyst and iodoacetate (IOAc) as the oxidant. Systematic kinetic isotope studies imply a mechanistic regime shift as the number of bonds separating the directing heteroatom and the target C–H bond increases. Both isotope and electronic effects observed in remote C–H bond activation are consistent with an electrophilic palladation pathway in which the initial palladation is slower than the C–H bond cleavage.



## 1. Introduction

Development of synthetically useful C–H bond activation reactions has received considerable interest in recent years.[1] In particular, palladium catalysts have been extensively used in $sp^2$ and $sp^3$ C–H bond functionalizations.[2] While direct hydrocarbon C–H functionalization remains a significant challenge,[3] chelation-assisted stoichiometric metal insertion into inert C–H bonds, namely cyclometalation, is relatively well-established.[4] C–H cleavages directed by heteroatom-containing functional groups such as oximes,[5] oxazolines,[6] pyridines,[7] and amides[8] have been extensively explored. Various approaches using simple functionalities such as *N*-Boc,[9] carboxyl,[10,11] and amino[12] groups as directing groups have also been developed. These chelates share a common feature of forming a five-membered palladacycle with the proximal C–H bonds separated by three bonds from the coordinating atoms as a prelude to the subsequent functionalization.[13] However, palladium-catalyzed activation of C–H bonds farther away from the directing group remains a difficult problem. Activation of such remote C–H bonds would require the formation of six- or higher-membered palladacycles, hitherto only little is known in the realm of chelation-assisted palladium-catalyzed C–H bond functionalizations (Scheme 1).[14,15] Furthermore, the mechanism of palladium-catalyzed C–H bond activation has primarily focused on the formation of five-membered palladacycles.[16] Both isotope and electronic effects have been used to investigate the mechanistic subtleties. However, lack in the general methodology to functionalize remote C–H bonds has prevented the evaluation of such mechanistic pathways in the activation of C–H bonds that would involve the formation of six- or higher-membered palladacycles. Herein we report a palladium-catalyzed *ortho*-iodination of aryl C–H bonds that are located four, five and six bonds away from the directing heteroatom. Systematic kinetic isotope studies imply a change in mechanism as the number of bonds separating the directing heteroatom and the target C–H bond increases.




**Scheme 1.** Activation of remote C–H bonds.

Selective functionalizations of remote C–H bonds have represented a great challenge in organic synthesis since the term 'remote functionalization' was coined by Breslow in the seventies.[17] While such processes are common to enzymes that anchor a functional group and recognize a specific site of the substrate,[18] these strategies are rarely reported in solution chemistry where such principles

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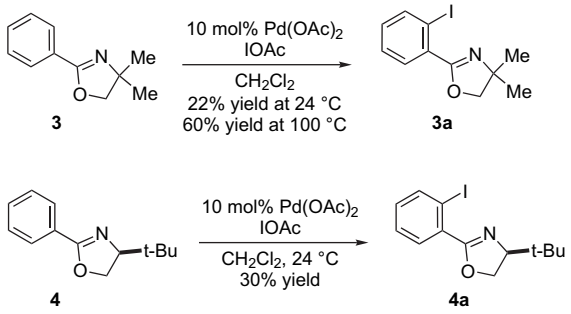
may be applied. Crabtree et al.[19] have recently uncovered a remarkable example of molecular recognition by a synthetic catalyst that selects a reaction site on carboxylic acid substrates through hydrogen bonding mimicking enzymatic reactions. Directed C–H activation has long been practiced for remote functionalization in electrophilic[20] radical processes without the assistance of metal catalysts. Oxidation of specific remote C–H bonds on steroid skeletons is achieved via a radical relay mechanism by attaching an iodoaryl template to the substrate.[21] Corey and Hertler have described an efficient and selective method for functionalizing a remote $C_{18}$ angular methyl group by the free radical chain decomposition of an *N*-chloro-20-aminosteroid in acid solution.[22] Suárez reagent ($I_2$/iodobenzene diacetate) has also been widely used to functionalize remote C–H bonds in steroids where a hydroxyl[23] or amide[24] group functions as a radical inductor under photochemical conditions. An alkylborane intermediate obtained from the hydroboration of tetrasubstituted alkenes with $BH_3\cdot THF$ has been shown to intramolecularly activate a remote C–H bond.[25] However, the remote activation of C–H bonds by transition metals is very rare. Few examples of remote C–H bond activation by 'naked' $Fe^+$, $Mn^+$, $Co^+$, and $Cr^+$ ions (ligand and counterion-free) in the gas phase have been reported by Schwarz[26] where functional groups such as nitrile,[27] isonitrile,[28] amine,[29] ketone,[30] alcohol,[31] alkyne,[32] and allene[32c] provide an anchor to the metal ions. Such an inadequate investigation into transition metal-catalyzed remote C–H bond activations provided the impetus to develop our iodination reaction[6c] for remote functionalization.

## 2. Results and discussion

### 2.1. Remote C–H bond activation

Recently, we found that the β-methyl groups of aliphatic carboxylic acids could be iodinated via $sp^3$ C–H bond activation under mild conditions using oxazoline as the auxiliary and IOAc[33] as the terminal oxidant.[6c] Considering the broad utility of aryl iodides in a variety of organic reactions,[34] we anticipated that the *ortho*-iodinated aryl carboxylic acids could provide synthetically valuable building blocks. However, the initial attempts to functionalize simple oxazoline **3** derived from benzoic acid gave poor yields under the standard reaction conditions (Scheme 2).[6c] We believe that the five-membered palladacycle intermediate resulting from *ortho*-palladation could be very stable and consequently not reactive toward the oxidant. Accordingly, the reaction temperature was increased to 100 °C and the mono-iodinated product **3a** was obtained in 60% yield. Enhancing the steric bulkiness of the palladacycle by using *tert*-butyl oxazoline **4** only increased the product yield marginally.




**Scheme 2.** Iodination of unactivated aryl C–H bonds.

We reasoned that six- or seven-membered cyclometalated complexes could be more reactive since they would make Pd(IV) intermediates less stable and hence the reductive elimination faster.[35] Indeed the five-membered cyclopalladated Pd(IV) complexes are remarkably stable and isolable.[35] Thus, substrates with the target C–H bonds separated from the directing group by four to six bonds were selected to test for the palladium-catalyzed remote C–H bond functionalization. Stirring the substrate **9** with 10 mol% $Pd(OAc)_2$ and 2 equiv of IOAc in $CH_2Cl_2$ at room temperature for 72 h provided the selectively mono-iodinated product **9a** in 95% isolated yield through the activation of *ortho*-aryl C–H bonds involving a six-membered palladacycle (Table 1, entry 5). The iodination protocol was also applicable for the substrates **12** and **13** in which the target C–H bonds are separated from the directing group by five and six bonds, respectively (Table 1, entries 8–10). Although 2-*tert*-butyl-4,4-dimethyloxazoline can be iodinated on the methyl group through a five-membered palladacycle at mild temperature,[6a] the aryl C–H bonds are preferred over the methyl C–H bonds in general even if seven- and eight-membered palladacycles are involved.

The yields can be increased at the expense of the selectivity for mono- and di-iodinations by raising the reaction temperature to 100 °C (Table 1, entry 10). We also found that yields are improved when sterically bulky oxazoline is employed as the directing group (Table 2, entries 1–3).

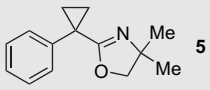
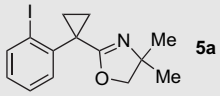
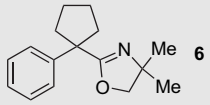
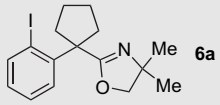
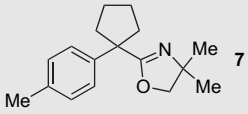
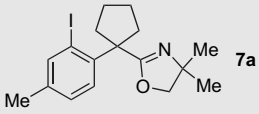
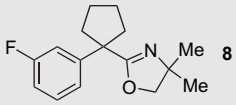
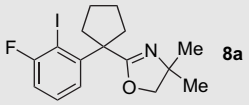
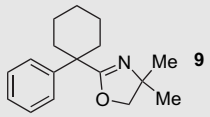
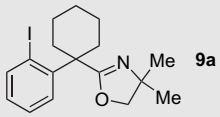
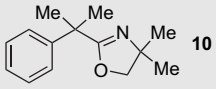
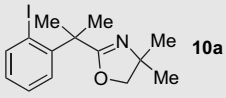
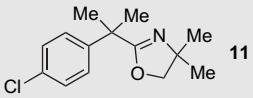
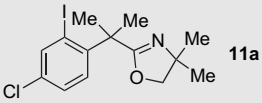
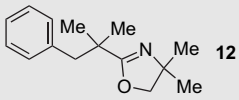
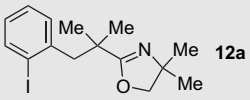
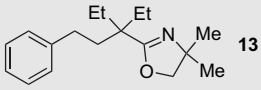
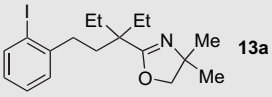
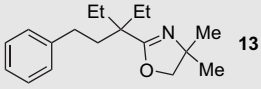
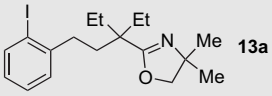
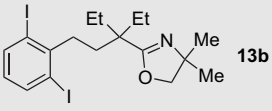
### 2.2. Mechanistic investigation

Extensive effort has been invested in determining the mechanistic pathway for the activation of C–H bonds leading to the formation of metalacycles. However, the exact nature of the activation step, especially whether it involves electrophilic activation, carbopalladation,[36] oxidative addition,[37] or σ-bond metathesis,[38] remains the subject of debate. Ryabov et al. proposed an electrophilic mechanism via the Wheland intermediate for the palladium-promoted cyclometalation of dimethylbenzylamine in which the acetate acts as an intramolecular base for deprotonation through a six-membered transition state **18** (Scheme 3).[16] A similar work on imine cyclometalation has, however, suggested a four-membered transition state **19**.[39]

Canty and van Koten have proposed the likelihood of oxidative addition of the aryl C–H bond to the electrophilic palladium(II) to form a palladium(IV) intermediate in which the acetate may or may not participate as a base.[40] Crabtree has put forward the intermediacy of agostic C–H complex or transition state **20** in which the $sp^2$ C–H bond being broken assumes an out-of-plane formation by partial rehybridization to $sp^3$ (Scheme 4).[41] The involvement of an agostic C–H complex and the participation of the acetate as an intramolecular base via a six-membered transition state have been further supported by computational studies in the case of cyclometalation by palladium acetate.[42] Milstein et al. have indeed characterized by X-ray analysis an $\eta^2$ aromatic C–H agostic complex, which can be deprotonated by weak organic bases to give the corresponding cyclometalated product.[43]

Investigation into the mechanism of C–H bond activation by palladium catalysts using physical organic approaches has primarily focused on the formation of five-membered palladacycles.[16] Both isotope and electronic effects have been used to support one pathway over the others. Our current remote iodination protocol has provided us an opportunity to evaluate these mechanistic pathways to the palladium-catalyzed functionalization of remote C–H bonds. We anticipated that the remote C–H bond activation may go through a different pathway[44] from that of the five-membered cyclopalladation process. We carried out a systematic intramolecular isotope effect on the *ortho*-iodination of substrates **21**–**24** (Scheme 5). The large intramolecular isotope effect ($k_H/k_D$=3.5) with substrate **21** is consistent with the previous reports on cyclopalladation reactions.[15f,g,45] Interestingly, the value of the intramolecular isotope effect gradually decreases to 1.0 when the

**Table 1**
Pd-catalyzed iodination of remote aryl C–H bonds at room temperature[a]

| Entry | Substrate | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **5** |  **5a** | 15 |
| 2 |  **6** |  **6a** | 81 |
| 3 |  **7** |  **7a** | 76 (91)[c] |
| 4 |  **8** |  **8a** | 86 |
| 5 |  **9** |  **9a** | 95 |
| 6 |  **10** |  **10a** | 72 |
| 7 |  **11** |  **11a** | 58 (65)[c] |
| 8 |  **12** |  **12a** | 40[d] |
| 9 |  **13** |  **13a** | 29 |
| 10 |  **13** |  **13a**<br>  **13b** | 87[e] (a/b 2:1) |

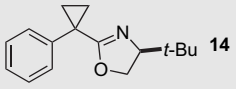
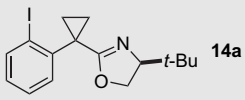
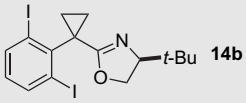
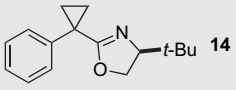
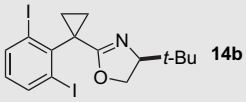
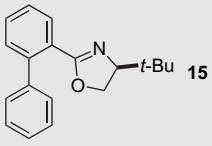
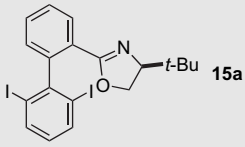
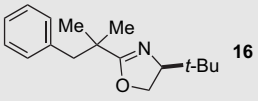
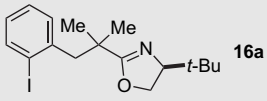
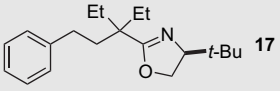
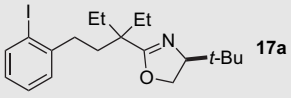
[a] $Pd(OAc)_2$ (10 mol %), IOAc (2 equiv), 24 °C, 72 h.
[b] Isolated yield.
[c] In parenthesis: microwave, 100 °C, 2 h.
[d] Unidentified side product (30%).
[e] Condition: 100 °C, 24 h.

C–H bonds are further away from oxazoline groups as shown by substrates **21**–**24**; a clear indication of the mechanistic regime shift for the activation of remote C–H bonds.

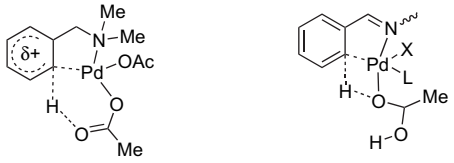
While this intriguing data may prompt a number of interpretations, we further carried out a brief study on electronic effects in the parent substrate **16** (Scheme 6). Previous study of electronic effects on C–H bond activation has focused on those substrates in which the coordinating ability of the directing group is also influenced by the substituents on the aryl ring.[45] This influence could complicate the interpretation of the electronic effects. The current remote C–H activation protocol has allowed an unprecedented investigation into the electronic effects on C–H bond activation (Fig. 1) in which the directing group is independent of any electronic perturbation in the aryl moiety. The negative slope of the Hammett plot ($\sigma=-1.6$) with substrate **16** ($k_H/k_D=1.5$) and its derivatives **25**–**27** indicates that electron-donating groups facilitate the cyclometalation process in the activation of the remote C–H bonds (Fig. 2).

The large value of the intramolecular isotope effect alone is insufficient to define whether a particular type of mechanism, such as an electrophilic activation or carbopalladation, is operative in the functionalization of proximal C–H bonds since the initial palladation process can be reversible and faster than the C–H bond cleavage in both cases. An alternative mechanism for the

**Table 2**
Pd-catalyzed iodination of remote aryl C–H bonds at room temperature using chiral oxazoline[a]

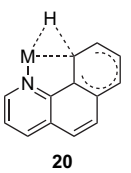
| Entry | Substrate | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **14** |  **14a**<br>  **14b** | 85[c] (a/b 4:1) |
| 2 |  **14** |  **14b** | 77[d] |
| 3 |  **15** |  **15a** | 79[e] |
| 4 |  **16** |  **16a** | 70[f] |
| 5 |  **17** |  **17a** | 38 |

[a] $Pd(OAc)_2$ (10 mol %), IOAc (2 equiv), 24 °C, 72 h.
[b] Isolated yield.
[c] IOAc (0.6 equiv), 50 h.
[d] 16 h.
[e] 24 h, 24 °C, 16 h.
[f] IOAc (0.5 equiv).

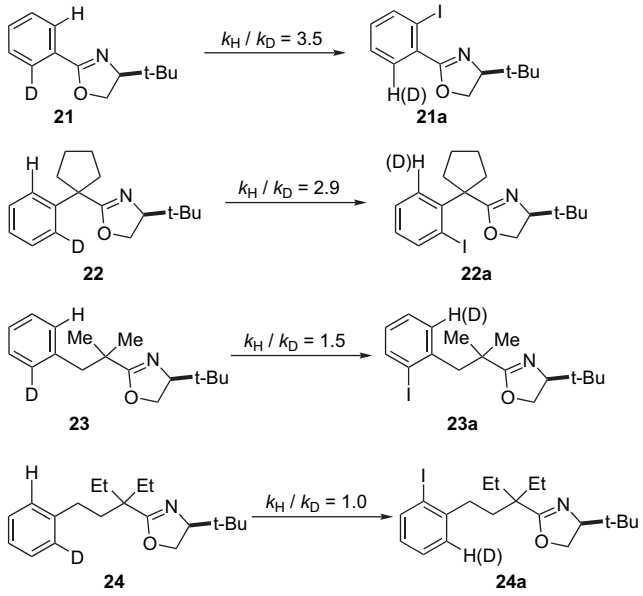



**Scheme 3.** Deprotonation by intramolecular acetate as a base.

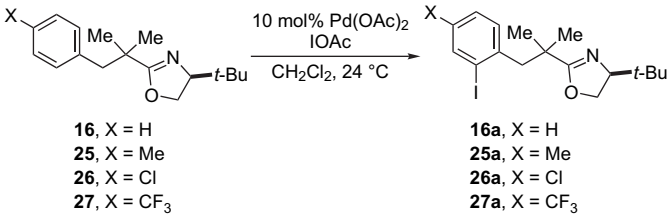
functionalization of proximal C–H bonds would be an oxidative addition or σ-bond metathesis. However, the complete loss of intramolecular isotope effect in the functionalization of the remote C–H bonds implies that the oxidative addition and σ-bond metathesis pathways, which involve a direct scission of the C–H bonds, are less likely to be operative.[46] Therefore, the electrophilic mechanism can be invoked to explain the observed results. The experimental observations can be rationalized based on the fact that, unlike the proximal C–H bonds, the remote C–H bonds have a high degree of freedom and the reaction system would have to compensate for the high entropy cost to bring the target C–H bond in proximity to the palladium. In other words, the palladation process during the electrophilic activation of the remote C–H bond




**Scheme 4.** Agostic C–H complex.




**Scheme 5.** Isotope effects on proximal and remote C–H bond activation.




**16**, X = H
**25**, X = Me
**26**, X = Cl
**27**, X = $CF_3$

**16a**, X = H
**25a**, X = Me
**26a**, X = Cl
**27a**, X = $CF_3$

**Scheme 6.** Iodination of substrates with substituents *meta* to the target C–H bonds.

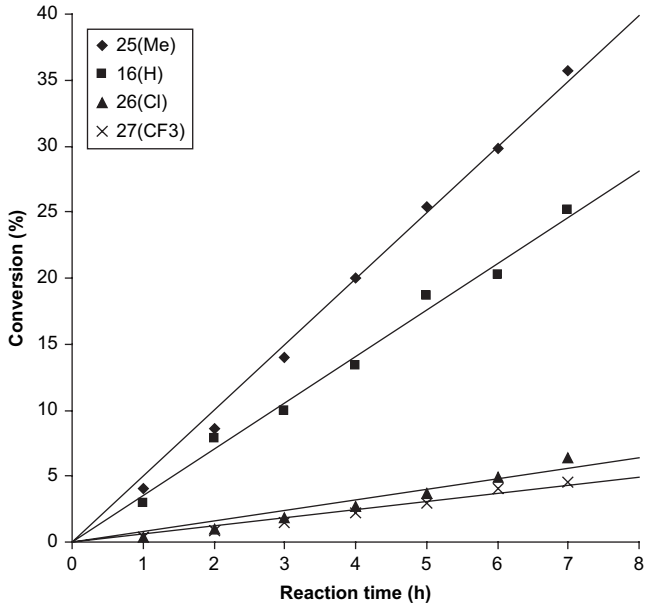



**Figure 1.** Electronic effect on the rate of remote C–H bond activation.

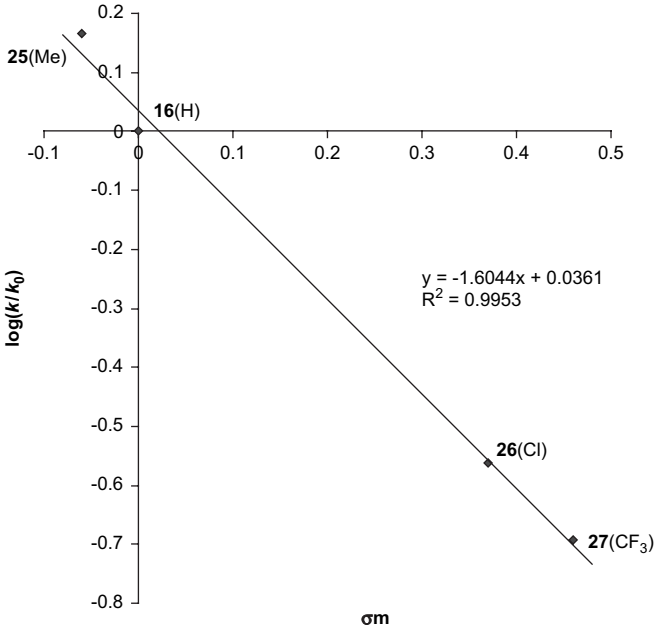



**Figure 2.** Hammett plot in the iodination of remote C–H bonds.

is likely to be slower than C–H cleavage. The negative slope of the Hammett plot ($\sigma=-1.6$) with substrate **16** ($k_H/k_D=1.5$) and its derivatives **25**–**27** further indicates that the electrophilic palladation can be operative for the activation of the remote C–H bonds.

## 3. Conclusions

Iodination of aryl C–H bonds located four, five or six bonds away from the directing group has been achieved using palladium acetate as the catalyst and IOAc as the oxidant. The current remote iodination protocol has allowed an unprecedented investigation into the mechanism of remote C–H bond activation. Systematic kinetic isotope studies imply a mechanistic regime shift as the number of bonds separating the directing heteroatom and the target C–H bond increases. Although the mechanisms for the activation of proximal C–H bonds are still uncertain, our experimental results suggest that an electrophilic pathway in which the initial palladation is slower than the C–H bond cleavage can be operative in the palladium-catalyzed functionalization of remote aryl C–H bonds.

## 4. Experimental

### 4.1. General experimental

Solvents were obtained from Acros and used directly without further purification. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian instrument (400 and 100 MHz, respectively) and internally referenced to the $SiMe_4$ signal. Exact mass spectra for new compounds were recorded on a VG 7070 high-resolution mass spectrometer. Analytical GC–MS was performed on a Hewlett–Packard G1800C instrument connected to an electron ionization detector using an MS-5 GC column (30×0.25 mm). Infrared spectra were recorded on a Perkin–Elmer FT-IR Spectrometer.

Carboxylic acids were purchased from Aldrich and Acros, and were used as received without further purification. $PhI(OAc)_2$ was procured from Acros. $Pd(OAc)_2$ and $I_2$ were received from Aldrich. The carboxylic acids for substrates **12**, **16**, and **25**–**27** were prepared by [1,3] sigmatropic rearrangement of the corresponding ketene silyl acetals and subsequent hydrolysis.[47] Carboxylic acids for substrates **13** and **17** were prepared by ethylation[48] of 4-phenylbutyric acid.

### 4.2. Preparation of oxazoline substrates

Carboxylic acids were converted to their acid chlorides using either oxalyl chloride[47] (**3**, **4**, **6**, **9**, and **10**) or thionyl chloride[49] (**5**, **7**, **8**, **11**–**17**, and **25**–**27**). The acid chlorides were then reacted with 2-amino-2-methyl-1-propanol or (*S*)-*tert*-leucinol to form amides,[50] which were subsequently cyclized to oxazolines using triphenylphosphine.[51]

### 4.3. General procedure for palladium-catalyzed *ortho*-iodination of remote C–H bonds

Oxazoline (0.2 mmol) was placed in a 20-mL scintillation vial and dissolved in $CH_2Cl_2$ (1 mL). Palladium acetate (4.4 mg, 0.02 mmol), iodobenzene diacetate (64.4 mg, 0.2 mmol), and iodine (50.7 mg, 0.2 mmol) were added to the solution. The vial was tightly sealed with a polypropylene lined cap and the resulting violet solution was stirred at the specified temperature until black palladium iodide precipitated out. The solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography eluting first with hexane to remove iodine and iodobenzene, and then with ethylacetate/hexane 1:20.

*Microwave-assisted protocol*: in a 20-mL septum-capped microwave vial (Microwave model: Discover® LabMate™), oxazoline (0.2 mmol), palladium acetate (2.2 mg, 0.01 mmol), iodobenzene diacetate (64.4 mg, 0.2 mmol), and iodine (50.7 mg, 0.2 mmol) were dissolved in $CH_2Cl_2$ (1 ml) under atmospheric air. The vial was stirred at 100 °C for 2 h at 100 W. The solvent was removed in a rotary evaporator. The product was purified by silica gel column

chromatography eluting first with hexane to remove iodine and iodobenzene, and then with ethylacetate/hexane 1:20.

*4.3.1. 2-(2-Iodophenyl)-4,4-dimethyl-4,5-dihydrooxazole (**3a**)*

Palladium iodide precipitated out at 72 h and **3a** was obtained as an orange-red oil (13.5 mg, 22% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (s, 6H), 4.15 (s, 2H), 7.10 (td, $J$=7.6, 1.6 Hz, 1H), 7.37 (td, $J$=7.2, 1.2 Hz, 1H), 7.57 (dd, $J$=7.6, 1.4 Hz, 1H), 7.90 (dd, $J$=8, 1.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 28.2, 68.2, 79.4, 94.7, 127.8, 130.5, 131.5, 134.2, 140.1, 162.8; IR (neat) $\nu$ 2918, 1656, 1585, 1462, 1308, 1082, 1016, 963 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{13}INO$ ($MH^+$) 302.0042, found 302.0027.

*4.3.2. (S)-4-tert-Butyl-2-(2-iodophenyl)-4,5-dihydrooxazole (**4a**)*

Palladium iodide precipitated out at 72 h and **4a** was obtained as an orange-red oil (19.7 mg, 30% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.02 (s, 9H), 4.13 (dd, $J$=10, 8.4 Hz, 1H), 4.26 (t, $J$=8.2 Hz, 1H), 4.39 (dd, $J$=10.4, 8.4 Hz, 1H), 7.098 (td, $J$=7.6, 1.7 Hz, 1H), 7.37 (t, $J$=7.6 Hz, 1H), 7.62 (dd, $J$=7.2, 2 Hz, 1H), 7.93 (d, $J$=7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 26.1, 34.1, 69.0, 76.8, 94.7, 127.8, 130.7, 131.5, 133.9, 140.5, 163.7; IR (neat) $\nu$ 2955, 1658, 1586, 1477, 1353, 1305, 1244, 1095, 1014, 963, 903, 760 cm$^{-1}$; HRMS (EI) calcd for $C_{13}H_{17}INO$ ($MH^+$) 330.0355, found 330.0342.

*4.3.3. 2-(1-(2-Iodophenyl)cyclopropyl)-4,4-dimethyl-4,5-dihydrooxazole (**5a**)*

Palladium iodide precipitated out at 72 h and **5a** was obtained as an orange-red oil (10.2 mg, 15% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18 (s, 2H), 1.26 (s, 6H), 1.73 (s, 2H), 3.88 (s, 2H), 6.94–7.01 (m, 1H), 7.30–7.35 (m, 2H), 7.85 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.0, 28.2, 28.6, 67.2, 79.6, 103.5, 128.0, 128.9, 131.8, 139.5, 143.2, 166.7; IR (neat) $\nu$ 2967, 2927, 1655, 1498, 1364, 1329, 1192, 1137, 1082, 933 cm$^{-1}$; HRMS (EI) calcd for $C_{14}H_{17}INO$ ($MH^+$) 342.0355, found 342.0340.

*4.3.4. 4,5-Dihydro-2-(1-(2-iodophenyl)cyclopentyl)-4,4-dimethyloxazole (**6a**)*

Palladium iodide precipitated out at 72 h and **6a** was obtained as a pale yellow solid (59.5 mg, 81% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31 (s, 6H), 1.64–1.70 (m, 2H), 1.82–1.92 (m, 2H), 2.18–2.28 (m, 2H), 2.57–2.67 (m, 2H), 3.91 (s, 2H), 6.90 (td, $J$=7.3, 1.9 Hz, 1H), 7.32 (td, $J$=7.6, 1.2 Hz, 1H), 7.38 (dd, $J$=8.0, 1.6 Hz, 1H), 7.94 (dd, $J$=7.8, 1.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.5, 28.0, 37.8, 54.7, 67.2, 79.5, 98.6, 127.7, 127.7, 128.1, 142.1, 146.0, 169.0; IR (neat) $\nu$ 2932, 1655, 1468, 1120, 971 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{21}INO$ ($MH^+$) 370.0668, found 370.0666.

*4.3.5. 2-(1-(2-Iodo-4-methylphenyl)cyclopentyl)-4,4-dimethyl-4,5-dihydrooxazole (**7a**)*

Palladium iodide precipitated out at 25 °C after 72 h and **7a** was obtained as an orange-red oil (58.5 mg, 76% yield) after purification by column chromatography. The title compound **7a** was also obtained in 91% isolated yield by heating the reaction mixture at 100 °C for 2 h under microwave. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31 (s, 6H), 1.60–1.73 (m, 2H), 1.79–1.91 (m, 2H), 2.15–2.24 (m, 2H), 2.25 (s, 3H), 2.54–2.65 (m, 2H), 3.91 (s, 2H), 7.11 (d, $J$=7.6 Hz, 1H), 7.25 (d, $J$=8.0 Hz, 1H), 7.78 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.1, 24.4, 28.03, 37.9, 54.3, 67.2, 79.5, 98.5, 127.3, 128.5, 138.0, 142.6, 142.9, 169.2; IR (neat) $\nu$ 2962, 2872, 1654, 1478, 1460, 1363, 1192, 1137, 1003, 965, 813 cm$^{-1}$; HRMS (EI) calcd for $C_{17}H_{23}INO$ $(MH)^+$ 384.0824, found 384.0832.

*4.3.6. 2-(1-(3-Fluoro-2-iodophenyl)cyclopentyl)-4,4-dimethyl-4,5-dihydrooxazole (**8a**)*

Palladium iodide precipitated out at 72 h and **8a** was obtained as an orange-red oil (66.8 mg, 86% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33 (s, 6H), 1.65–1.75 (m, 2H), 1.83–1.95 (m, 2H), 2.13–2.23 (m, 2H), 2.56–2.66 (m, 2H), 3.96 (s, 2H), 6.74 (td, $J$=8.2, 3.2 Hz, 1H), 7.12 (dd, $J$=11.0, 3.0 Hz, 1H), 7.85 (dd, $J$=8.6, 6.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.4, 28.0, 37.8, 54.7, 67.3, 79.5, 91.2 (d, $J_F$=3.8 Hz, 1C), 115.5 (d, $J_F$=49.4, 22.8 Hz, 1C), 143.0 (d, $J_F$=7.5 Hz, 1C), 148.6 (d, $J_F$=6.9 Hz, 1C), 161.4, 163.8, 168.5; IR (neat) $\nu$ 2963, 2872, 1656, 1596, 1577, 1456, 1271, 1015, 1002, 878, 864, 809 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{20}FINO$ ($MH^+$) 388.0574, found 388.0574.

*4.3.7. 4,5-Dihydro-2-(1-(2-iodophenyl)cyclohexyl)-4,4-dimethyloxazole (**9a**)*

Palladium iodide precipitated out at 72 h and **9a** was obtained as a pale yellow solid (72.7 mg, 95% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.34 (s, 6H), 1.40–1.61 (m, 4H), 1.74–1.85 (m, 2H), 2.17–2.26 (m, 2H), 2.36–2.45 (m, 2H), 3.92 (s, 2H), 6.88 (td, $J$=7.5, 1.6 Hz, 1H), 7.34 (t, $J$=7.8 Hz, 1H), 7.50 (dd, $J$=8.4, 1.6 Hz, 1H), 7.96 (dd, $J$=7.8, 1.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 22.6, 25.8, 28.1, 34.6, 46.7, 67.2, 78.7, 96.8, 127.8, 128.0, 128.7, 143.0, 145.3, 168.7; IR (neat) $\nu$ 2929, 2863, 1655, 1462, 1452, 1363, 1249, 1112, 1004, 975 cm$^{-1}$; HRMS (EI) calcd for $C_{17}H_{23}INO$ ($MH^+$) 384.0824, found 384.08411.

*4.3.8. 2-(2-(2-Iodophenyl)propan-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**10a**)*

Palladium iodide precipitated out at 72 h and **10a** was obtained as an orange-red oil (49.7 mg, 72% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33 (s, 6H), 1.73 (s, 6H), 3.97 (s, 2H), 6.91 (td, $J$=7.6, 1.7 Hz, 1H), 7.35 (td, $J$=7.6, 1.2 Hz, 1H), 7.43 (dd, $J$=8.0, 1.2 Hz, 1H), 7.94 (dd, $J$=8.0, 1.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.8, 28.0, 43.6, 67.3, 79.56, 97.7, 127.1, 128.3, 128.3, 142.3, 146.2, 169.9; IR (neat) $\nu$ 2973, 2889, 1658, 1462, 1384, 1363, 1296, 1112, 1008, 974, 931, 757 cm$^{-1}$; HRMS (EI) calcd for $C_{14}H_{19}INO$ ($MH^+$) 344.0511, found 344.0499.

*4.3.9. 2-(2-(4-Chloro-2-iodophenyl)propan-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**11a**)*

Palladium iodide precipitated out at 25 °C after 48 h and **11a** was obtained as an orange-red oil (44.1 mg, 58% yield) after purification by column chromatography. The title compound **11a** was also obtained in 65% isolated yield by heating the reaction mixture at 100 °C for 2 h under microwave. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.32 (s, 6H), 1.70 (s, 6H), 3.97 (s, 2H), 7.31–7.33 (m, 2H), 7.93 (d, $J$=2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 27.8, 28.0, 43.3, 67.4, 79.6, 97.5, 127.7, 128.2, 132.9, 141.4, 144.9, 169.5; IR (neat) $\nu$ 2926, 2855, 1660, 1364, 1295, 1125, 1110, 1022, 974, 817 cm$^{-1}$; HRMS (EI) calcd for $C_{14}H_{18}ClINO$ ($MH^+$) 378.0122, found 378.0114.

*4.3.10. 2-(1-(2-Iodophenyl)-2-methylpropan-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**12a**)*

Palladium iodide precipitated out at 72 h and **12a** was obtained as a pale yellow oil (28.6 mg, 40% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.26 (s, 6H), 1.27 (s, 6H), 3.11 (s, 2H), 3.96 (s, 2H), 6.87 (t, $J$=7.6 Hz, 1H), 7.15–7.25 (m, 2H), 7.83 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 26.1, 28.7, 38.8, 48.9, 67.2, 79.1, 103.2, 128.0, 128.3, 130.5, 130.6, 140.0, 170.66; IR (neat) $\nu$ 2929, 2358, 1560, 1496, 1456, 1266, 876, 668 cm$^{-1}$; GC–MS ($M^+$) found 357.

*4.3.11. 2-(3-Ethyl-1-(2-iodophenyl)pentan-3-yl)-4,4-dimethyl-4,5-dihydrooxazole (**13a**)*

Palladium iodide precipitated out at 25 °C after 72 h and **13a** was obtained as pale yellow oil (23.2 mg, 29% yield) after purification by column chromatography. The title compound **13a** was also obtained in 58% isolated yield by heating the reaction mixture at 100 °C for 24 h. Diiodinated product **13b** was also observed in

29% yield by $^1$H NMR and was not isolated. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$=7.6 Hz, 6H), 1.30 (s, 6H), 1.68 (q, $J$=7.6 Hz, 4H), 1.74–1.80 (m, 2H), 2.55–2.62 (m, 2H), 3.93 (s, 2H), 6.86 (t, $J$=7.4 Hz, 1H), 7.15–7.24 (m, 2H), 7.78 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 8.2, 26.5, 28.7, 34.7, 35.6, 43.2, 67.0, 78.6, 100.3, 127.6, 128.4, 129.4, 139.4, 145.3, 169.4; IR (neat) $\nu$ 2927, 2361, 1557, 1496, 1454, 1259, 1049, 874, 824, 668 cm$^{-1}$; GC–MS ($M^+$) found 399. The title compound **13a** was also obtained as a pale yellow oil (23.2 mg, 29% yield) when the reaction was carried out at room temperature.

#### *4.3.12. (S)-4-tert-Butyl-2-(1-(2-iodophenyl)cyclopropyl)-4,5-dihydrooxazole (**14a**)*

The title compound **14a** was obtained when the reaction was carried out with 0.6 equiv of IOAc under the standard reaction conditions. Palladium iodide precipitated out at 50 h and **14a** was obtained as a pale yellow solid (48.1 mg, 65% yield) along with **14b** (12.6 mg, 17.1% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.87 (s, 9H), 1.12–1.19 (m, 1H), 1.20–1.28 (m, 1H), 1.67–1.75 (m, 1H), 1.76–1.84 (m, 1H), 3.79 (dd, $J$=10, 6.8 Hz, 1H), 4.00–4.13 (m, 2H), 6.97 (td, $J$=7.1, 2.6 Hz, 1H), 7.28–7.35 (m, 2H), 7.85 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 18.6, 26.0, 28.7, 34.0, 69.3, 75.6, 103.0, 128.0, 128.8, 132.3, 139.4, 143.3, 168.1; IR (neat) $\nu$ 2953, 2917, 1660, 1468, 1434, 1361, 1157, 1014, 983, 929 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{21}INO$ ($MH^+$) 370.0668, found 370.0651.

#### *4.3.13. (S)-4-tert-Butyl-2-(1-(2,6-diiodophenyl)cyclopropyl)-4,5-dihydrooxazole (**14b**)*

The title compound **14b** was also obtained as a pale yellow solid (76 mg, 77% yield) when the reaction was carried out under the standard condition using 2.0 equiv of IOAc. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (s, 9H), 1.17–1.30 (m, 2H), 1.97–2.09 (m, 2H), 3.80 (dd, $J$=9.6, 6.8 Hz, 1H), 4.03–4.14 (m, 2H), 6.59 (t, $J$=8.0 Hz, 1H), 7.88 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.3, 25.9, 33.1, 34.1, 69.3, 75.7, 103.4, 103.6, 129.9, 140.0, 144.0, 166.7; IR (neat) $\nu$ 2952, 2898, 1659, 1539, 1475, 1415, 1360, 1160, 1101, 981, 767 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{20}I_2NO$ ($MH^+$) 495.9634, found 495.9614. The title compound **14b** was also obtained as a pale yellow solid (76 mg, 77% yield) when the reaction was carried out under the standard condition using 2 equiv of IOAc.

#### *4.3.14. (S)-4-tert-Butyl-2-(2′,6′-diiodobiphenyl-2-yl)-4,5-dihydrooxazole (**15a**)*

Palladium iodide precipitated out at 24 h and **15a** was obtained as a pale yellow solid (83.9 mg, 79% yield) after purification by column chromatography. $^1$H NMR (400 MHz, CDCl3) $\delta$ 0.74 (s, 9H), 3.84 (dd, $J$=9.8, 8.6 Hz, 1H), 3.95 (t, $J$=8.6 Hz, 1H), 4.12 (dd, $J$=9.8, 8.6 Hz, 1H), 6.63 (t, $J$=8.0 Hz, 1H), 7.08 (d, $J$=8.0 Hz, 1H), 7.48 (td, $J$=7.6, 1.2 Hz, 1H), 7.56 (td, $J$=7.5, 1.2 Hz, 1H), 7.86 (m, 2H), 7.99 (d, $J$=8.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.9, 33.8, 68.1, 76.6, 98.0, 98.7, 126.3, 128.3, 129.4, 129.8, 130.1, 130.7, 138.1, 148.0, 150.2, 161.2; IR (neat) $\nu$ 3059, 2955, 2902, 1654, 1540, 1477, 1416, 1352, 1249, 1191, 1040, 969, 901, 773 cm$^{-1}$; HRMS (EI) calcd for $C_{19}H_{20}I_2NO$ ($MH^+$) 531.9634, found 531.9645.

#### *4.3.15. (S)-4-tert-Butyl-2-(1-(2-iodophenyl)-2-methylpropan-2-yl)-4,5-dihydrooxazole (**16a**)*

Palladium iodide precipitated out at 16 h and **16a** was obtained as a pale yellow oil (54.0 mg, 70% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.88 (s, 9H), 1.27 (s, 6H), 3.13 (d, AB, $J$=14.2 Hz, 2H), 3.84 (dd, $J$=10, 7.2 Hz, 1H), 4.10 (t, $J$=8.0 Hz, 1H), 4.19 (t, $J$=9.4 Hz, 1H), 6.83–6.89 (m, 1H), 7.17–7.25 (m, 2H), 7.83 (d, $J$=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.7, 25.8, 33.8, 38.8, 48.6, 68.4, 75.4, 103.1, 127.8, 128.0, 130.5, 139.8, 141.5, 172.0; IR (neat) $\nu$ 2956, 2927, 1662, 1466, 1364, 1124, 1010, 981, 917 cm$^{-1}$; HRMS (EI) calcd for $C_{17}H_{25}INO$ ($MH^+$) 386.0981, found 386.0973.

#### *4.3.16. (S)-4-tert-Butyl-2-(3-ethyl-1-(2-iodophenyl)pentan-3-yl)-4,5-dihydrooxazole (**17a**)*

Palladium iodide precipitated out at 72 h and **17a** was obtained as an orange-red oil (32 mg, 38% yield) after purification by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.84–0.91 (m, 6H), 0.92 (s, 9H), 1.63–1.72 (m, 4H), 1.73–1.80 (m, 2H), 2.59–2.66 (m, 2H), 3.88 (dd, $J$=12.0, 7.6 Hz, 1H), 4.04 (t, $J$=8.2 Hz, 1H), 4.16 (dd, $J$=10.4, 8.4 Hz, 1H), 6.86 (td, $J$=7.6, 2.0 Hz, 1H), 7.16–7.25 (m, 2H), 7.78 (dd, $J$=7.8, 1.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 8.4, 26.8, 26.8, 33.6, 35.1, 35.7, 43.5, 67.9, 75.7, 100.3, 127.6, 128.4, 129.5, 139.4, 145.5, 170.7; IR (neat) $\nu$ 2961, 2902, 1658, 1466, 1363, 1122, 984 cm$^{-1}$; HRMS (EI) calcd for $C_{20}H_{31}INO$ ($MH^+$) 428.1450, found 428.1440.

### 4.4. General procedure for the measurement of kinetic isotope effects on the rate of *ortho*-iodination of remote aryl C–H bonds

The deuterated oxazoline substrates **21**–**24** were prepared as follows.[52] To a stirred solution of the corresponding mono-iodinated oxazoline (0.2 mmol) and $Cu_2Cl_2$ (19.8 mg, 0.1 mmol) in MeOH-$d_4$ (1 ml) was added $NaBD_4$ (1.2 mmol) in small portions over a period of 30 min at 0 °C. After stirring for 10 min, the resulting black precipitate was removed by filtration and the filtrate was concentrated in a rotary evaporator. The product was purified by silica gel column chromatography eluting with ethylacetate/hexane 1:20.

Deuterated oxazoline (0.1 mmol) was placed in a 20-mL scintillation vial and dissolved in $CH_2Cl_2$ (1 mL). Palladium acetate (2.2 mg, 0.01 mmol), iodobenzene diacetate (32.2 mg, 0.1 mmol), and iodine (25.4 mg, 0.1 mmol) were added to the solution. The vial was tightly sealed with a polypropylene lined cap and the resulting violet solution was stirred at room temperature. The reactions were terminated at 1, 2, 3, 4, 5, 6, and 7 h and the products were analyzed by $^1$H NMR. The reactions were carried out in triplicates and the average value was used for plotting the graph.

### 4.5. General procedure for the measurement of the electronic effects on the rate of *ortho*-iodination of remote aryl C–H bonds and the Hammett plot

Oxazoline substrate **16**, **25**, **26** or **27** (0.1 mmol) was placed in sealed NMR tubes and dissolved in $CD_2Cl_2$ (1 mL). Palladium acetate (2.2 mg, 0.01 mmol), iodobenzene diacetate (32.2 mg, 0.1 mmol), and iodine (25.4 mg, 0.1 mmol) were added to the solution. The NMR tubes were tightly sealed and the resulting violet solution was stirred at room temperature. The reactions were monitored at 1, 2, 3, 4, 5, 6, and 7 h by $^1$H NMR. The reactions were carried out in triplicates and the average value was used for plotting the graph.

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