LETTER

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Activation of remote *meta*-C–H bonds assisted by an end-on template

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Functionalization of unactivated carbon–hydrogen (C–H) single bonds is an efficient strategy for rapid generation of complex molecules from simpler ones. However, it is difficult to achieve selectivity when multiple inequivalent C–H bonds are present in the target molecule. The usual approach is to use *σ*-chelating directing groups, which lead to *ortho*-selectivity through the formation of a conformationally rigid six- or seven-membered cyclic pre-transition state[1–14]. Despite the broad utility of this approach, proximity-driven reactivity prevents the activation of remote C–H bonds. Here we report a class of easily removable nitrile-containing templates that direct the activation of distal *meta*-C–H bonds (more than ten bonds away) of a tethered arene. We attribute this new mode of C–H activation to a weak 'end-on' interaction[15] between the linear nitrile group and the metal centre. The 'end-on' coordination geometry relieves the strain of the cyclophane-like pre-transition state of the *meta*-C–H activation event. In addition, this template overrides the intrinsic electronic and steric biases as well as *ortho*-directing effects with two broadly useful classes of arene substrates (toluene derivatives and hydrocinnamic acids).

The development of new transformations in which inert C–H bonds react as dormant functional groups holds great promise for expediting organic synthesis by providing unprecedented retrosynthetic disconnections. In this endeavour, controlling the positional selectivity of C–H cleavage in molecules that contain multiple C–H bonds is an outstanding challenge that must be addressed before widespread synthetic applications. Currently, *σ*-chelation-directed metalation of C–H bonds has been used as a powerful means of achieving *ortho*-selectivity[1–6]. Diverse carbon–carbon and carbon–heteroatom bond-forming reactions with broadly useful substrates have recently been developed using Pd(II)[7–9], Rh(III)[10–13], and Ru(II)[14] catalysts. In directed C–H activation, assembly of a conformationally rigid cyclic pre-transition state is required (**I** in Fig. 1a), which introduces two inherent limitations. First, despite extensive and innovative efforts towards remote C–H functionalization reactions[15–18], the difficulties associated with forming a macrocyclic pre-transition state larger than a seven-membered ring generally preclude the activation of remote C–H bonds. Second, the high energy associated with well-defined cyclophane-like pre-transition states prevents *meta*- or *para*-selective C–H activation reactions (**II** in Fig. 1a). Although significant progress has been made in the development of *meta*- and *para*-selective C–H functionalization reactions[19–27], the positional selectivity is largely governed by steric (1,3-substituted arenes)[19,20], or electronically biased (mono-substituted arenes)[20–25] properties of the arene substrates. A generally applicable approach for remote *meta*-C–H activation that controls positional selectivity by overriding the intrinsic electronic

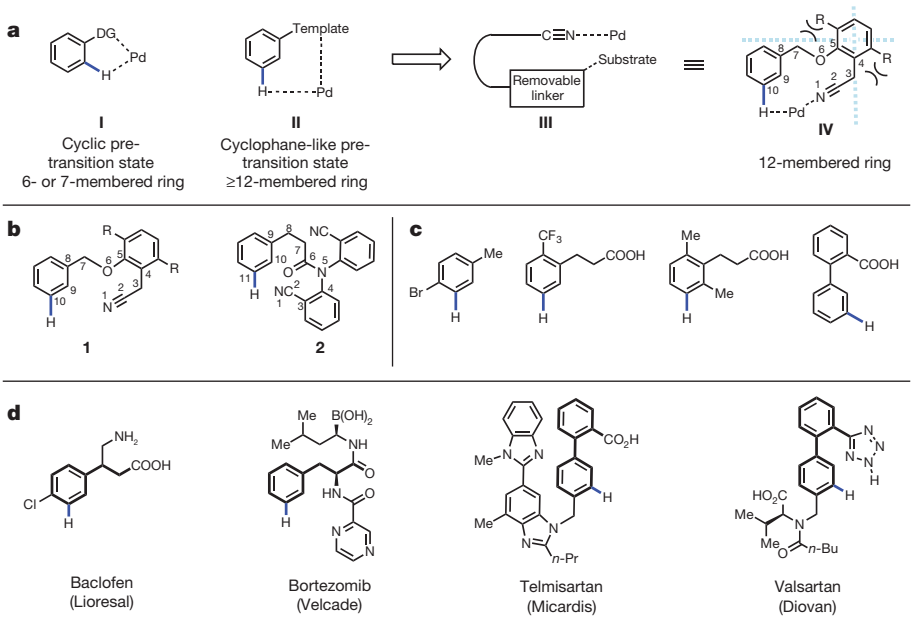

Figure 1 | A template strategy for the activation of distal *meta*-C–H bonds (more than ten bonds away). a, Remote *meta*-C–H activation is a challenge. I: *ortho*-directed C–H activation. DG, directing group. II, III and IV: Remote *meta*-C–H activation using an 'end-on' template. The dotted blue lines divide the arene template into four quadrants. The blue bonds in all figures highlight the targeted C–H bonds. **b**, Templates for toluenes and hydrocinnamic acids. **c**, Unprecedented positional selectivity in C–H activation, overriding electronic and steric biases, and *ortho*-directing effects.. **d**, Structurally related drug molecules (brand names in parentheses).

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and steric properties of arene substrates, especially mono-substituted arenes, has remained a challenge.

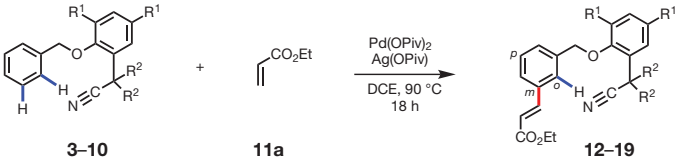
Here we report the discovery of a class of nitrile-containing templates that deliver palladium to the vicinity of tethered arene substrates to promote C–H olefination of distal *meta*-C–H bonds with excellent selectivity (Fig. 1). This linear 'end-on' coordinating nitrile group[15] is proposed to accommodate a macrocyclic cyclophane-like pre-transition state, thus overcoming the inherent limitations of traditional directed C–H activation. We demonstrate the generality of this template approach with two categorically different classes of substrates (toluene and hydrocinnamic acid derivatives **1** and **2**) (Fig. 1b). Remarkably, the template overrides the intrinsic electronic and steric biases as well as *ortho*-directing effects of the arene substrates, consistently securing high *meta*-selectivity in most cases (Fig. 1c). This *meta*-selective C–H olefination reaction is also compatible with *ortho*,*ortho*-disubstituted arene and 2-biphenylcarboxylic acid substrates. Both hydrocinnamic and 2-biphenylcarboxylic acids are key structural motifs in many drug molecules, including the $GABA_B$ receptor agonist drug Baclofen (Fig. 1d).

Considering that the major limitations of directed C–H activation arise from the stringent requirement of assembling a rigid cyclic pre-transition state, we began to devise a removable chelating template that would recruit the Pd(II) catalyst through a less rigid assembly involving reversible weak coordination. We suspected that the weakly binding end-on nitrile group would either make the cyclophane-like pre-transition state less strained or would lead to release of the Pd(II) catalyst in the vicinity of the target C–H bond, thereby providing high effective concentration (**III** in Fig. 1a). The latter 'catch and release' scenario would obviate the need to assemble a cyclophane-like pre-transition state all together. Although weak coordination is not as effective as strong coordination in terms of compensating for the entropic cost during the assembly of the pre-transition state, the nitrile-bound Pd(II) centre is more reactive because it is highly electrophilic, which is beneficial for C–H activation. We also anticipated that the linear coordination mode of the nitrile group would be more likely to anchor the palladium to the *meta* position rather than the *ortho* position. In this putative structure, the interaction with the *ortho*-C–H bond would incur high levels of cyclophane ring strain caused by the linear geometry of the nitrile group. Encouragingly, Schwarz's pioneering studies showed that this mode of end-on coordination of alkyl nitriles with Fe(II) in the gas phase can guide the metal to perform remote C–H activation[15].

To put this hypothesis into practice, we engineered a nitrile-containing template in which the substrate was attached through a removable benzyl ether linkage (**IV** in Fig. 1a). At the outset, we hypothesized that the flat arene would help to keep the substrate moiety and nitrile group as coplanar as possible. Given that the plane in which the arene template lies could be spatially divided into four distinct quadrants (see **IV** in Fig. 1a), we further hypothesized that sterically bulky *tert*-butyl groups at the *ortho* positions of the arene template could serve as blocking groups to ensure that the pendant substrate and the nitrile group were kept in the same quadrant to achieve high effective concentration of the Pd(II) catalyst. In our first design, we used a nitrile-containing phenol as the template, which could easily be attached to benzyl bromide to give benzyl ether **3** as the model substrate for testing *meta*-selective C–H activation (Table 1).

Using olefination of **3** as the model reaction[28,29], we extensively screened catalysts, oxidants and solvents (see Supplementary Information) and found that a combination of $Pd(OPiv)_2$ as the catalyst and AgOPiv as the oxidant gave a 15% yield with encouraging levels of *meta*-selectivity (*m*:*p*:*o* = 59:33:8) (Table 1, entries 1–3). To improve the reactivity further via the Thorpe–Ingold effect, we installed two alkyl groups at the α-position adjacent to the nitrile group. Both the yield and the *meta*-selectivity steadily improved with increasing size of the alkyl groups (entries 4–8). The isobutyl-substituted template gave a

Table 1 | Optimization of template



Entry	Substrate	R^1	R^2	Yield (%) (mono)	Yield (%) (di)	Selectivity (*meta*:*para*:*ortho*)
1	**3**	*tert*-butyl	H	Trace	0	—
2	**3**	*tert*-butyl	H	4	0	56:26:18
3	**3**	*tert*-butyl	H	15	0	59:33:8
4	**4**	*tert*-butyl	Methyl	60	17	91:7:2
5	**5**	*tert*-butyl	Ethyl	52	16	93:6:1
6	**6**	*tert*-butyl	$-(CH_2)_4-$	50	11	88:7:5
7	**7**	*tert*-butyl	$-(CH_2)_5-$	51	15	91:5:4
8	**8a**	*tert*-butyl	Isobutyl	63	20	95:4:1
9	**9**	H	Isobutyl	—	—	—
10	**10**	Methyl	Isobutyl	39	10	91:8:1

The reaction scheme is shown above the table. Unless otherwise noted, the reaction conditions were as follows: benzyl ethers **3**–**10** (0.05 mmol), olefin **11a** (1.5 equiv.), $Pd(pivalate)_2$ (10 mol%), Ag-pivalate (2.1 equiv.), 1,2-dichloroethane (0.5 ml), 90 °C, 18 h. The isolated yield was obtained by silica gel column chromatography. The ratio of *meta*:*para*:*ortho* mono-olefinated products was determined by ^1H NMR analysis of the unpurified reaction mixture; the variance is estimated to be within 5%. For entry 1, O_2 was used as the oxidant instead of Ag-pivalate. For entry 2, $Pd(OAc)_2$ and AgOAc were used instead of $Pd(OPiv)_2$ and AgOPiv respectively and NMR yield was determined by using *o*-xylene as an internal standard. For entry 9, C–H olefination occurred on both the arene substrate and template with a combined yield of approximately 20% yield.

mixture of mono- and di-olefinated products $\mathbf{17a_{mono}}$ and $\mathbf{17a_{di}}$ in 83% combined yield (entry 8). The mono- and di-olefinated products can be readily separated by chromatography. Importantly, the *meta*-selectivity was found to be 95%. We also confirmed through control experiments that the presence of the bulky *tert*-butyl blocking groups on the template was essential for reactivity (entries 9, 10). Replacement of the nitrile by a methyl group also resulted in complete loss of reactivity and selectivity (see Supplementary Information).

With this newly established *meta*-selective C–H olefination procedure in hand, we carried out olefination on a variety of substituted arenes (Fig. 2). *Meta*-substituted arenes were olefinated at the remaining *meta* position with excellent selectivity regardless of the electronic properties of the substituents (**17b**–**g**). With *ortho*-substituted arene substrates, high *meta*-selectivity was also achieved with both an electron-donating methyl group and electron-withdrawing fluoro and bromo groups (**17h**–**j**). Notably, in the absence of the template, the *para*- and *meta*-C–H bonds of these 1,2-substituted arene substrates are often difficult to distinguish, yet the template directed *meta*-C–H activation with high selectivity. For example, *meta*-selective olefination places the newly installed functional group at the position *para* to the bromo group, which is synthetically enabling owing to the diverse reactivities of the bromo group (**17j**). Despite the steric hindrance, *para*-substituted arenes are also olefinated at the *meta*-position in excellent selectivity (**17k**–**n**). In sharp contrast to previously reported *meta*-selective C–H functionalization reactions[21], the template also effectively overrides the electronic effect of bromide or ester groups at the *para* position, affording predominantly the *meta*-olefinated products (**17m**, **17n**). Intriguingly, the template can guide the catalyst to reach and activate the *meta*-C–H bond in a selective manner in the presence of *ortho*,*ortho*-di-fluoro substitution (**17o**). *Meta*-C–H functionalization of *ortho*,*ortho*-disubstituted arenes provides a powerful disconnection for constructing 1,2,3,4-tetrasubstituted arenes. Finally, *meta*-C–H olefination of naphthalene **8p** also proceeded to give **17p** in 79% yield.

We next extensively surveyed the scope of the olefin coupling partners. Olefination with commonly used electron-deficient α,β-unsaturated esters, ketones and phosphonates gave desired products in good yields ($\mathbf{17b_2}$–$\mathbf{b_5}$). Given that the lack of reactivity with disubstituted olefins in directed C–H olefination reactions is a significant drawback[28,29], we tested a series of di- or tri-substituted olefins. We were pleased to find that olefination with all of these olefins proceeded

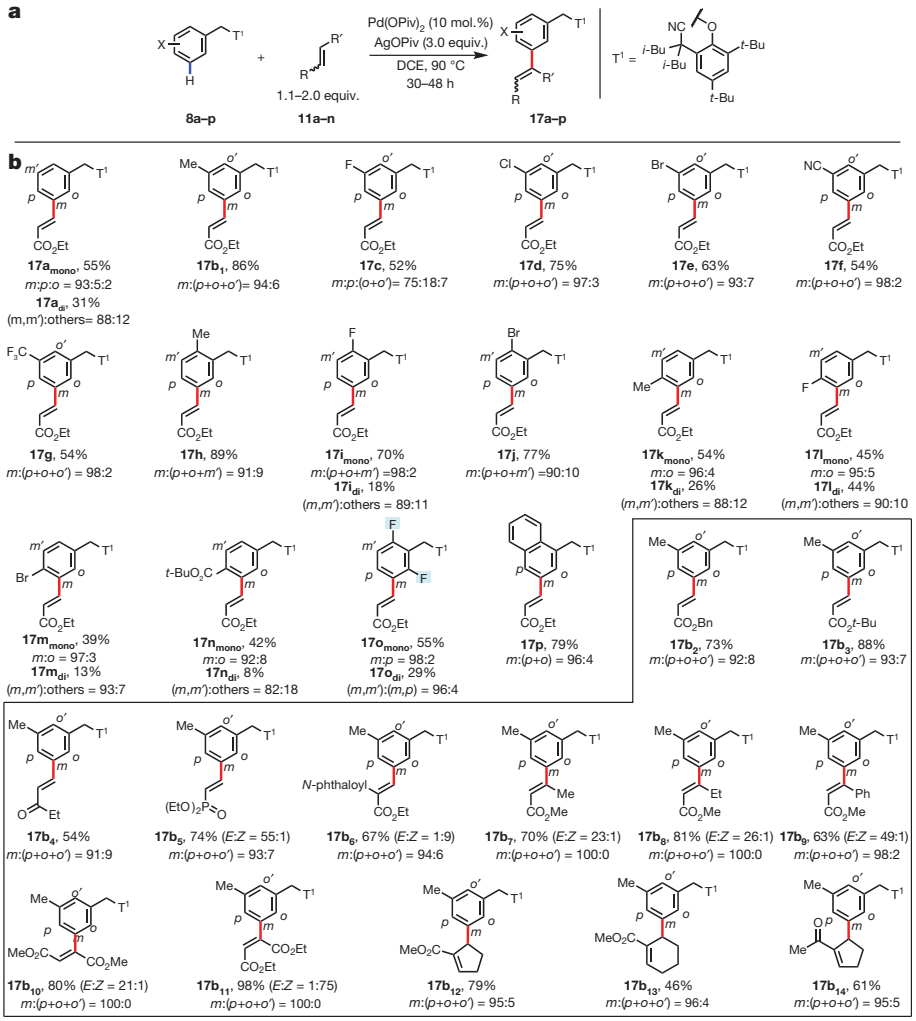


Figure 2 | Template-directed *meta*-selective C–H olefination of toluene derivatives. **a**, Arenes (**8a**–**p**) with a variety of substitution patterns undergo facile olefination. **b**, In the box, many election-deficient olefins and various di- and tri-substituted olefins were used. The isolated yield of the mono-olefinated product (and also the isolated yield of the di-olefinated product when applicable) is shown along with the selectivity. See Supplementary Information for experimental details. Selectivity of the mono- and di-olefinated products was determined by ^{1}H NMR analysis and confirmed by one-dimensional selective NOESY experiments; the variance is estimated to be within 5%. OPiv, pivalate.

stereoselectively[30] to give the trisubstituted olefins (**17b$_6$**–**b$_{14}$**) in moderate to excellent yields. For example, olefination products **17b$_{10}$** and **17b$_{11}$** were formed when diethyl maleate and diethyl fumarate were used respectively. Unlike in conventional directed *ortho*-C–H olefination reactions where the coordinated directing group could prevent sterically hindered olefins from binding[28,29], in this case the nitrile group on the template is weakly coordinated to the [Pd(II)–Ar] intermediate and can be effectively displaced by disubstituted olefins, allowing carbopalladation to proceed. Lastly, we found that the template could be readily removed through a Pd/C-mediated hydrogenolysis to afford *meta*-alkylated toluenes in excellent yields (see Supplementary Information).

Having demonstrated the concept of using a nitrile-containing end-on template to activate *meta*-C–H bonds that are ten bonds away from the chelating atom, we tested whether this approach would be generally applicable to other broadly useful substrates, after appropriate tuning of the template. Therefore, we used a readily cleavable amide linkage to attach a benzonitrile template to hydrocinnamic acid to form **20a**. Using the established olefination protocol from above (Fig. 2), we screened various reaction parameters with substrate **20a** and observed significant solvent effects, presumably owing to the dramatic influence of the solvent medium on the assembly of the pre-transition state via weak coordination (see Supplementary Information). Olefination of **20a** in hexafluoroisopropanol gave *meta*-olefinated product **21a$_{mono}$** in 49% yield along with 11% *para*- and 2% *ortho*-olefinated products, as determined by ^{1}H nuclear magnetic resonance (NMR) analysis. To further improve the reactivity, we turned to mono-*N*-protected amino acid ligands, which were recently found to accelerate C–H olefination reactions[29]. We found through extensive ligand screening that *N*-acetyl-protected glycine was most effective in promoting the olefination reaction, allowing for full conversion to be achieved (see Supplementary Information). The *meta*-selectivity of the mono-olefinated product **21a$_{mono}$** was also enhanced from 79% to 95% (Fig. 3). Notably, highly *meta*-selective C–H functionalization of electronically unbiased monosubstituted arenes has not been reported so far[19–27]. Control experiments showed that replacement of the nitrile group on the template with a trifluoromethyl group resulted in poor reactivity and selectivity giving a *m:p:o* 1:1:2 mixture of mono-olefinated products in 38% yield under the optimized conditions.

The efficiency of this template was first demonstrated by the excellent observed reactivity with the electron-deficient *meta*-trifluoromethylarene **20b**. To showcase the power of the template in controlling the *meta*-selectivity, *meta*-methoxy and *ortho*-trifluoromethyl groups were introduced onto the aromatic rings (**20c** and **20d** respectively), two functional groups known to exert strong electronic effects on traditional electrophilic aromatic substitution reactions. Remarkably, excellent *meta*-selectivity was maintained in the olefination of both *meta*-methoxyarene **20c** and *ortho*-trifluoromethylarene **20d** to give **21c**

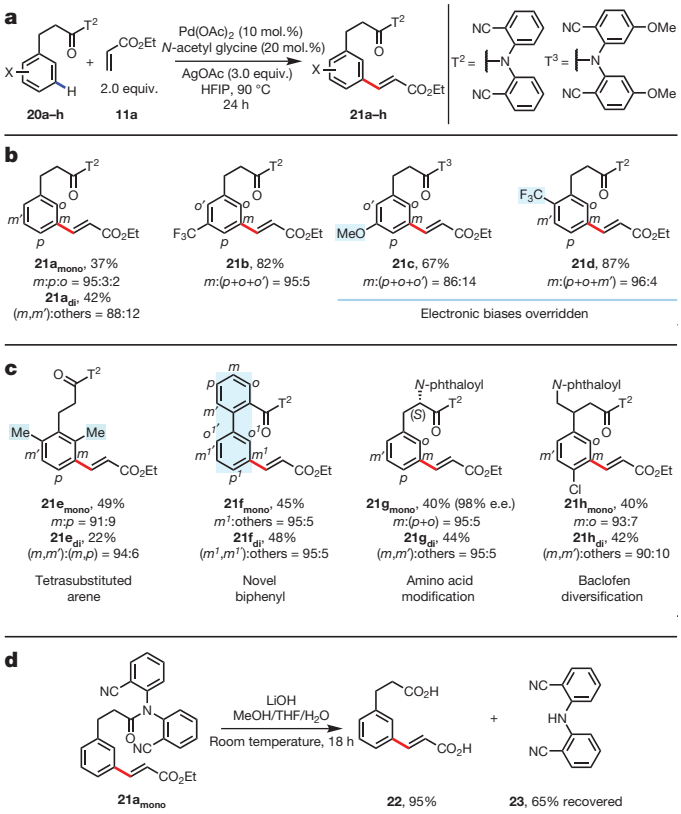


Figure 3 | Template-directed *meta*-selective C–H olefination of hydrocinnamic acid derivatives. **a**, Four representative hydrocinnamic acids (**20a–d**). **b**, Challenging substrates and synthetic applications. **c**, Removal of template under mild hydrolysis conditions. *S* denotes the absolute configuration of the chiral centre; e.e., enantiomeric excess. The isolated yield of the mono-olefinated product (and also the isolated yield of the di-olefinated product when applicable) is shown along with the selectivity. Selectivity of the mono- and di-olefinated products was determined by ^{1}H NMR analysis and confirmed by one-dimensional selective NOESY experiments; the variance is estimated to be within 5%. See Supplementary Information for experimental details. HFIP, hexafluoroisopropanol. Room temperature was 24 °C.

and **21d** respectively, suggesting that the template effectively overrides the electronic effects of both electron-donating and -withdrawing groups. To further demonstrate the potential synthetic applications of this method, we first constructed a sterically encumbered tetrasubstituted arene **21e** via *meta*-selective olefination of the *ortho*,*ortho*-dimethylarene **20e**, in which case the steric hindrance was overcome by the template. Intriguingly, *meta*-selective C–H olefination of biphenyl substrate (**20f**) also proceeded at the remote aryl ring to afford synthetically useful biphenyl **21f** with unprecedented site-selectivity. Importantly, the unnatural chiral amino acid **21g** was also prepared via *meta*-selective olefination of *N*-phthaloyl-protected phenylalanine **20g** without racemization. Both 2-biphenylcarboxylic acid (**20f**) and phenylalanine (**20g**) are key structural motifs in drug molecules such as Micardis and Velcade. Finally, *N*-phthaloyl-protected Baclofen (**20h**) was selectively olefinated at the *meta*-position to give **21h** in 82% yield, providing access to a novel library of molecules of medicinal interest. The reactivity and selectivity patterns observed with **20a–h** have not been reported in previous studies towards *meta*-selective C–H activation[19–21]. To establish scalability, the reaction of **20d** was also run at the 0.5 g (1.2 mmol) scale to give **21d** in 77% yield. The removal of the template in **21a$_{mono}$** was readily accomplished by hydrolysis at room temperature using LiOH as a base to give diacid **22** in 95% yield (Fig. 3).

In summary, we have developed a template approach to activate remote *meta*-C–H bonds of two categorically distinct classes of substrates with high *meta*-selectivity. Template-assisted *meta*-selective C–H activation overrides *ortho*-directing effects as well as electronic and steric biases on the appended arene substrates. The template design is predicated on the weak interaction between Pd(II) and a nitrile group, where the nitrile group coordinates in an end-on fashion and can overcome the difficulties associated with assembling a cyclophane-like pre-transition state. This new strategy for directing remote C–H activation provides a novel route for the preparation of toluene derivatives, hydrocinnamic acids, 2-biphenylcarboxylic acids, unnatural amino acids, and drug molecules with sophisticated substitution patterns that are difficult to access using conventional C–H activation methods. We expect that this end-on nitrile-based template can be structurally modified to suit other classes of synthetically useful arene substrates.

METHODS SUMMARY

General procedure for template-directed *meta*-selective C–H olefination of toluene derivatives. A 15-ml sealed tube (with a Teflon cap) equipped with a magnetic stir bar was charged with substrate (46.1 mg, 0.10 mmol), $Pd(OPiv)_2$ (3.0 mg, 0.010 mmol, 0.10 equiv.), and AgOPiv (62.7 mg, 0.30 mmol, 3.0 equiv.). Ethyl acrylate (16.5 µl, 0.15 mmol, 1.5 equiv.) was added, followed by 1,2-dichloroethane (1.0 ml). The tube was then capped and submerged into a pre-heated 90 °C oil bath. The reaction was stirred for a total of 42 h and cooled to room temperature. The crude reaction mixture was filtered through a pad of Celite and washed with Et_2O (2 ml × 3). The filtrate was concentrated *in vacuo*, and the resulting residue was purified by column or preparative thin layer chromatography using hexanes/EtOAc as the eluent. The positional selectivity was determined by ^{1}H NMR of the unpurified reaction mixture. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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