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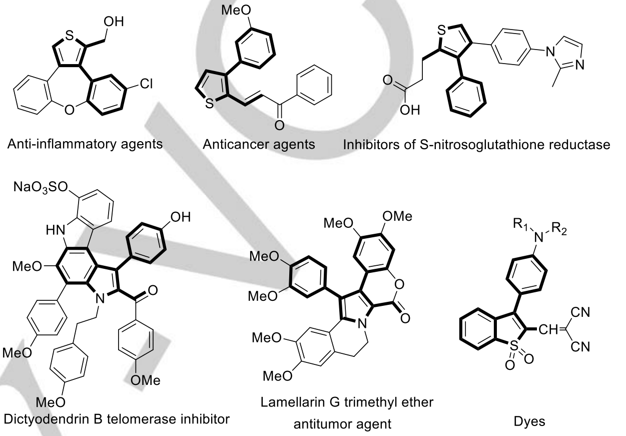
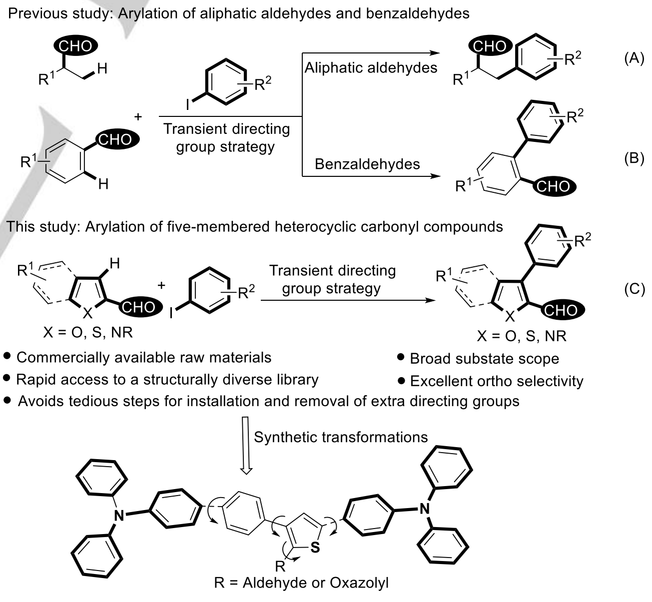
Transient Ligand Enabled *ortho*-Arylation of Five-Membered Heterocyclic Carbonyl Compounds: Facile Build-up of Mechanochromic Materials

Bijin Li, Kapileswar Seth, Ben Niu, Lei Pan, Huiwen Yang, and Haibo Ge*

Abstract: Reported herein is the first example of a direct arylation of heteroarenes *via* a transient ligand-directed strategy without the construction and deconstruction of a directing-group. A wide range of heteroarenes is able to undergo the coupling with diverse aryl iodides to assemble a large library of highly selective and functionalized 3-arylthiophene-2-carbaldehydes. This route provides an opportunity to rapidly build-up new mechanofluorochromic materials. Moreover, a novel strategy for mechanochromic luminogens with chromism trends of red- and blue-shift has been disclosed for the first time *via* facile functional group modifications on a common structural frame.



Scheme 1. Selected examples of pharmaceuticals, natural products, and organic functional material molecules containing *β*-aryl-substituted five-membered heterocyclic motifs.



Scheme 2. Direct arylation of aliphatic aldehydes, benzaldehydes and heteroaryl-aldehydes *via* transient ligand-directed strategy without the construction and deconstruction of a directing group.

The *β*-aryl-substituted five-membered heterocyclic motifs are privileged scaffolds in organic functional materials, bio-active compounds, and pharmaceuticals (Scheme 1).[1] In principle, *β*-aryl-substituted five-membered heterocyclic carbonyl compounds can be obtained by condensation reactions and classical transition metal-catalyzed C–X/C–B(OH)$_2$ Suzuki cross-coupling reactions.[2] However, tedious multiple-step synthesis and regioselectivity problems associated with these protocols significantly restrict/impede the rapid access to structurally diverse *β*-aryl-substituted five-membered heterocyclic carbonyl compounds.[2] Despite the recent advancement of transition metal catalyzed direct C–H arylation of heteroarenes, the development of a novel transition-metal catalytic system that can selectively arylate otherwise less reactive C–H bond on five-membered heterocycles is very important from both scientific and practical aspects.[3-4] For example, the Pd-catalyzed C–H bond arylation of thiophenes/pyrroles with haloarenes preferentially occurs at the *α*-positions to the sulfur/nitrogen atom (C2 and/or C5) due to the chemical reactivity of the thiophene/pyrrole ring.[5] However, selective and preferential arylation at the *β*-positions to the sulfur/nitrogen atom has rarely been documented, encouraging the design of an efficient strategy to accomplish such a challenge caused by the less reactive C–H bond on heteroarenes.[4b]

Recently, the use of a transient ligand as the directing group has emerged as a promising strategy in the field of oxidative C–H activation. The ligand can bind to the substrate and then coordinate to the metal centre in a reversible fashion, which bears inherent advantages of ready installation and easy removal without affecting the functionality of the substrate.[6-7] The direct arylation of aliphatic aldehydes and benzaldehydes *via* transient ligand-directed strategy has been reported (Scheme 2A-B).[7c,7f] To the best of our knowledge, the direct arylation of five-membered heterocyclic carbonyl compounds *via* transient ligand-directed strategy without the construction and deconstruction of a directing-group has not been previously described. Given the importance of *β*-aryl-substituted five-membered heterocyclic carbonyl compounds in organic functional materials, bio-active compounds, and pharmaceuticals, the transient ligand-directed strategy would be the most straightforward and efficient approach to access a large library of hetero-biaryls. In this context, we report a transient directing group based approach to accomplish direct C3 arylation of five membered heterocycles tethered to C2-carbonyls (Scheme 2C).

The optimization study of the reaction parameters was carried out using thiophene-2-carbaldehyde and iodobenzene as the substrates. For the detailed optimization of the reaction conditions, see the supporting information (Table S1). The screening of several parameters led us to the standard reaction condition as the use of 10 mol% Pd(OAc)$_2$, 40 mol% ligand, 3-

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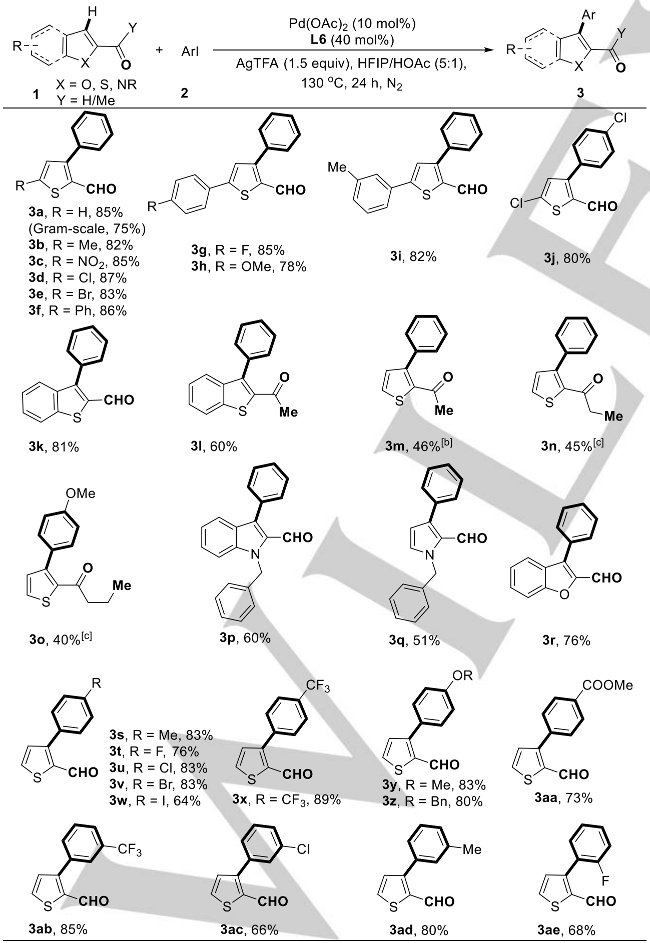
amino-3-methylbutanoic acid (**L6**) and 1.5 equiv. AgTFA in AcOH/HFIP (1/5, v/v) at 130 °C under atmospheric N_2, affording the desired arylated product 3-phenylthiophene-2-carbaldehyde (**3a**) in 85% isolated yield in 24 h. In addition, the reaction did not work without the amino acid ligand (entry 23, Table S1), highlighting the indispensable role of the transient ligand in forming the transient directing group as otherwise carbonyl oxygen alone could not act as directing atom for this transformation.

With the optimized condition in hand, a library of structurally diverse carbonyl tethered hetero-biaryls were synthesized using electronically different heterocyclic carbonyl compounds and aryl iodides (Table 1). It is noteworthy that **3a** could also be obtained on a gram scale in 75% yield. A wide range of heteroarenes including heteroaromatic aldehydes and ketones were found effective under the standard operation condition. The reaction showed high selectivity at the *ortho* position and no C5-arylation product was detected (**3m**-**3o**, **3q**, **3s**-**3ae**, Table 1). Furthermore, a variety of sensitive functional groups such as fluoro, chloro, bromo or iodo were well tolerated, enabling the scope of further synthetic transformations (Table 1). This work achieves direct site-selective arylation of heteroarenes *via* the transient directing group strategy without the construction and deconstruction of the directing-group. A plausible reaction pathway of this process is proposed (see the Supporting Information, Figure S1).[7c]

Table 1. The library of carbonyl containing hetero-biaryls[a]



3a, R = H, 85% (Gram-scale, 75%)
3b, R = Me, 82%
3c, R = NO_2, 85%
3d, R = Cl, 87%
3e, R = Br, 83%
3f, R = Ph, 86%

3g, R = F, 85%
3h, R = OMe, 78%

3i, 82%

3j, 80%

3k, 81%

3l, 60%

3m, 46%[b]

3n, 45%[c]

3o, 40%[c]

3p, 60%

3q, 51%

3r, 76%

3s, R = Me, 83%
3t, R = F, 76%
3u, R = Cl, 83%
3v, R = Br, 83%
3w, R = I, 64%

3x, R = CF_3, 89%

3y, R = Me, 83%
3z, R = Bn, 80%

3aa, 73%

3ab, 85%

3ac, 66%

3ad, 80%

3ae, 68%

[a] Reaction condition: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), ligand (9.36 mg, 0.08 mmol, 40 mol%), AgTFA (66.3 mg, 0.3 mmol, 1.5 equiv), HOAc (0.3 mL), HFIP (1.5 mL), 130 °C, N_2, 24 h. [b] Glycine (6.0 mg, 0.08 mmol, 40 mol%) was used as ligand. [c] $Pd(OAc)_2$ (5.4 mg, 0.024 mmol, 12 mol%), glycine (12.0 mg, 0.16 mmol, 80 mol%), 36 h.

Mechanofluorochromic materials are considered as "smart" stimuli-responsive materials, and are of great interests from both scientific and engineering viewpoints because of their potential applications in various areas including sensors, memory devices, and security systems, etc.[8-9] Currently, most of the reported organic mechanochromic materials showed a sole chromism trend of red- or blue-shift from external stimuli in the solid state. In comparison, there are only limited examples describing two different chromism trends.[8-9] The prediction of mechanochromism and its trend of luminogens is recognized as an appealing, yet challenging puzzle.[8-9] The mechanochromic properties of these materials mainly depend on efficient molecular packing which is governed by different intermolecular interactions such as hydrogen bond, π-π, and dipole-dipole interactions.[8b-c,9a,9r] Even though the examples describing mechanochromic properties are limited and the most reported cases have occurred as single isolated events but they have the common characteristics: the molecular packing modes are changed by mechanical forces that led to mechanochromic luminescent behavior.[8-9] The highly twisted conformation usually exists in the weak intermolecular interactions and relatively loose packing, which is easily affected by external mechanical forces to endow a chromism response.

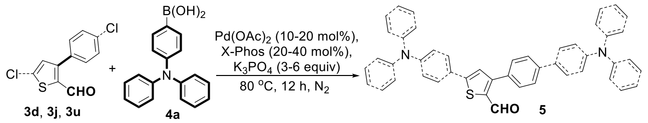
Triphenylamine (TPA) derivatives are considered as versatile materials because they possess good electron-donating property, hole-transporting capability and nonplanar characteristic.[10] We conceived that the aggregation behaviours of 3-aryl-(2-aldehyde)thiophenes could be restrained by incorporating TPA into the skeletons due to the propeller-like geometry of TPA, which may endow them with a strong emission and highly twisted conformation (Scheme 2). In this case, TPA group was used as the donor (D) moiety and aldehyde units as the acceptor (A) to construct donor–acceptor π-conjugated fluorescent dyes. These D–A systems may change D–A geometry upon perturbation to achieve responsive systems. On the other hand, the oxazoles as electron-withdrawing groups are often used to construct D–A molecules, which are important scaffolds in organic functional materials.[11] In view of different electron-withdrawing nature/properties and conformation effect of aldehyde and oxazole units which may influence mechanochromic behavior of chromophores, we attempt to obtain a counterpoint in chromism trends *via* simple conversion of aldehyde unit to oxazole on common TPA linked 3-aryl-(2-aldehyde)thiophenes framework.

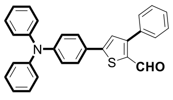
Following our design strategy, we next turned our attention toward the synthesis of 3-arylthiophene-2-carbaldehydes possessing electron-donating TPA functionality. Given that the transient ligand-directed protocol developed herein can tolerate the reactive chloride, the direct use of chloro substituted 3-aryl-(2-aldehyde)thiophenes as starting materials could avoid the tedious multiple-step synthesis and would greatly streamline synthetic routes. The palladium-catalyzed Suzuki cross-coupling of (4-(diphenylamino)phenyl)boronic acid with **3d**, **3u** and **3j** was performed to obtain the corresponding TPA derivatives **5a**, **5b** and **5c** (Table 2). In addition, the aldehyde group could be

10.1002/anie.201713357

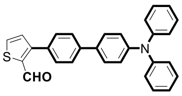
facially transformed into the oxazole functionality using the tosylmethylisocyanide and afforded the desired products in satisfactory yields (Table 3).

Table 2. Synthesis of TPA-bearing 3-phenyl-(2-carbaldehyde)thiophenes[a]

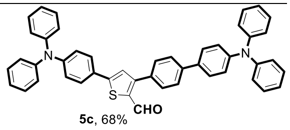




5a, 78%
481 nm,[b] 45%[b]
498 nm,[c] 570 nm[d]



5b, 76%
475 nm,[b] 38%[b]
516 nm,[c] 556 nm[d]

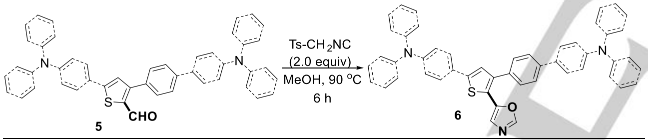


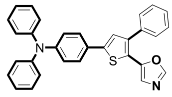
5c, 68%
485 nm,[b] 41%[b]
521 nm,[c] 565 nm[d]

[a] For detailed reaction conditions, see the supporting information. [b] Emission maximum and quantum yields in toluene (5×10^{-5} M). [c] Emission maximum in pristine powder. [d] Emission maximum in ground powder.

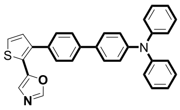
The photophysical properties of the synthesized library of 3-arylthiophene-2-oxazoles and 3-arylthiophene-2-carbaldehydes were measured with respect to emission maximum and quantum yields in toluene and emission maxima before and after grinding (Tables 2 and 3). As shown in Figure 1, their emission wavelengths in toluene are located in the range of blue to green region (425 nm to 521 nm), and remarkably high fluorescence quantum yields in toluene solution (38%-62%) have been observed. Their absorption and emission spectra in toluene are also shown in Figure S2 in Supporting Information.

Table 3. Synthesis of TPA-containing 3-phenyl-(2-oxazole)thiophenes[a]

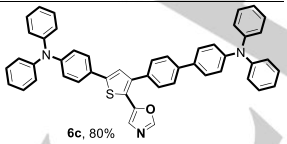




6a, 83%
439 nm,[b] 62%[b]
552 nm,[c] 447 nm[d]



6b, 84%
425 nm,[b] 55%[b]
504 nm,[c] 454 nm[d]



6c, 80%
455 nm,[b] 50%[b]
571 nm,[c] 478 nm[d]

[a] For detailed reaction conditions, see the supporting information. [b] Emission maximum and quantum yields in toluene (5×10^{-5} M). [c] Emission maximum in pristine powder. [d] Emission maximum in ground powder.

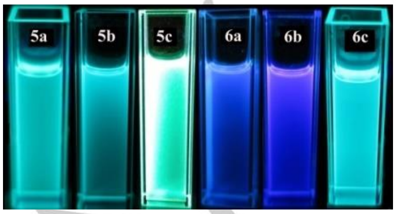


Figure 1. Fluorescence images of **5a**–**5c** and **6a**–**6c** in toluene (5.0×10^{-5} M) under UV light (365 nm).

The mechanochromic behaviors of these luminogens were further evaluated (Figures 2 and S3). As expected, all of the emission peaks of **5a-5c** were clearly red-shifted by grinding (approximately 72, 40, and 44 nm, respectively) (Figure 2; Figure S3 and S5). The pristine powder of **5a-5c** exhibited a blue/green emission upon excitation with UV lamp (λ_{ex} = 365 nm). Moreover, the emission of ground **5a-5c** exhibited a yellow emission (Figure S3; Table S2). It needs to be noted that the emission of **5a-5c** in toluene (λ_{em} = 475, 481, 485 nm) is very similar to their pristine powder (λ_{em} = 516, 498, 521 nm), while their ground powder displayed remarkable red-shift of emission. It is quite obvious that for **5a-5c**, the generation of a new aggregate during the grinding process led to red-shift of emission. We also analyzed single crystal structure of **5a**. As illustrated in Figure 3, **5a** displayed a highly twisted conformation and the π-π stacking mode. In the molecular structure of **5a**, the aldehyde group and TPA act as a weak acceptor and a moderate donor, respectively. The twisted conformation between *β*-phenyl and thienyl groups has the dihedral angles of 35.9° or 35.3°. The crystal structure of **5a** reveals 67.1-77.9° dihedral angle between the phenyl as a linker and the other two phenyls in the TPA, which demonstrates a twisted conformation of **5a**. Intermolecular C–H⋯O hydrogen bonds (3.359 Å) and C–H⋯C–H (3.380 Å) contacts were observed in the crystals. The shorter distance among phenyl planes of neighboring molecules indicated a potential π-π stacking.[9b] External force stimuli were able to induce conformation planarization of the twisted TPA moieties and strengthen intermolecular π-π stacking interactions, which were considered as the reasons for red-shifted emission.[9f]

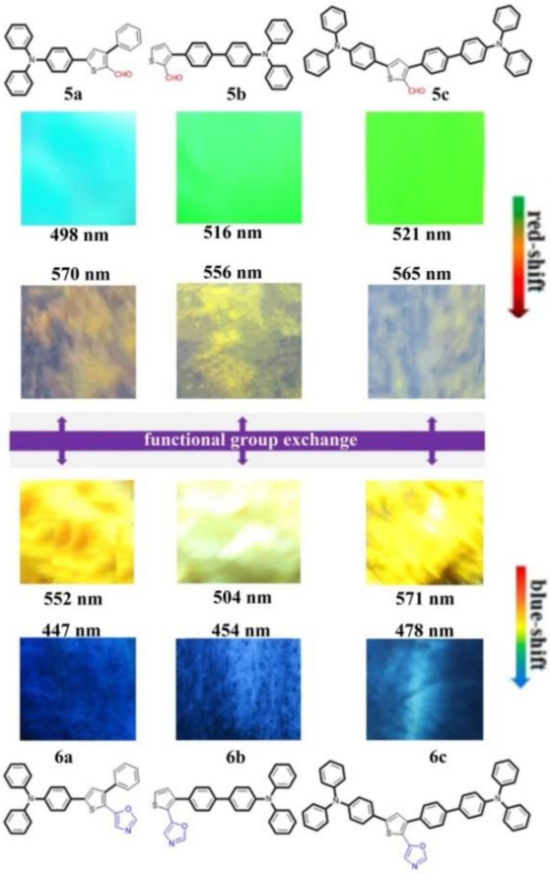


Figure 2. The fluorescent images of **5** and **6** before and after grinding.

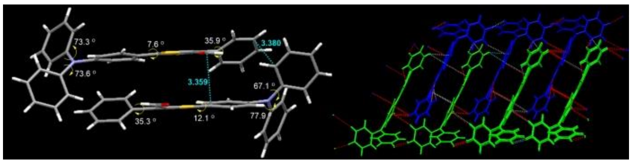


Figure 3. Crystal packing structure of **5a.**

In contrast, all oxazole derivatives **6a-6c** exhibited blue-shifted mechanochromic behaviors (Figure 2). The mechanofluorochromic behaviors of these compounds were further investigated in details. Grinding of the pristine powder **6a-6c** induced a substantial blue-shift with emission color change from yellow (λ_{em} = 504-571 nm) to blue (λ_{em} = 447-478 nm) (approximately 105, 50, and 93 nm, respectively) (Figure 2; Figure S3 and S6). These results reflect that the exchange of the aldehyde and oxazole moieties does make a counterpoint in chromism trends. The emission of ground powder **6a-6c** is similar to that in toluene. Thus, the fluorescence blue-shift after grinding the powder can be ascribed to weakened intermolecular π-π interactions. Significantly, ground powder **6b** and **6c** displayed deep-blue emission with CIE_{1931} of (0.15, 0.05) and (0.17, 0.06), which is very close to EBU coordinates of (0.15, 0.06) (Figure 2, Figure S4 and Table S2). These results indicate their promising applications in highly efficient standard-blue luminescent devices.[11]

To gain an in-depth understanding of the origin of the mechanochromic properties of **5a** and **6a** powder, we studied the phase characteristics of **5a** and **6a** powder by differential scanning calorimetry (DSC) and powder X-ray diffraction(PXRD) analysis. DSC experiment for the different states of **5a** displayed the ground samples present a slight exothermal peak, indicating a transition between the metastable state and the stable state (Figure S7). The PXRD patterns of the unground powder of **5a** showed sharp and intense reflection peaks, but these sharp peaks disappeared after grinding treatment. These experiments demonstrate a morphological transition from the crystalline to amorphous phases. The DSC and PXRD experiments on **6a** powder exhibited no obvious exothermal peak and diffraction peaks, suggesting that solid **6a** stays in an amorphous state and lacks close molecular packing (Figure S8).

In summary, a highly site-selective arylation reaction of five-membered heterocyclic carbonyl compounds with aryl iodides has been developed for the first time through a palladium-catalyzed C–H bond functionalization process with 3-amino-3-methylbutanoic acid as a transient ligand. This approach provides a straightforward access to 3-arylthiophene-2-carbaldehydes and 3-arylthiophene-2-oxazoles, which opens up a new avenue for rapid construction of mechanochromic materials. As results, a novel strategy for the blue- and red-shift mechanochromic luminogens has been developed based on TPA-containing β-aryl-substituted five-membered heterocyclic carbonyl compounds. The TPA-containing 3-arylthiophene-2-carbaldehydes displayed remarkable red-shift of emission. Interestingly, facile conversion of the aldehyde group to oxazole resulted in the blue-shifted luminogens. This represents the first example of achieving two different chromism trends on a common structural frame *via* a ready functional group change, and thus will inspire the development of novel applicable mechanochromic materials with rich stimuli responsive behavior.

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Keywords: five-membered heterocyclic carbonyl compounds • transient ligand • C-H activation • palladium-catalysis• mechanofluorochromic materials

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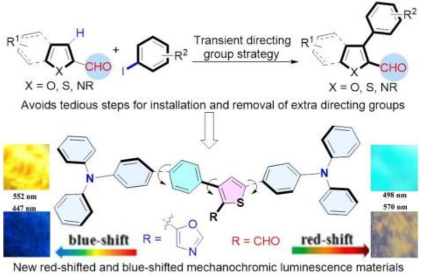
COMMUNICATION

The direct arylation of heteroarenes *via* a transient ligand-directed strategy has been developed, without the construction and deconstruction of the directing-group. The route provides an opportunity to rapidly build-up novel mechanofluorochromic materials.



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Page No. – Page No.

Transient Ligand Enabled *ortho*-Arylation of Five-Membered Heterocyclic Carbonyl Compounds: Facile Build-up of Mechanochromic Materials