ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 4038

Received 18th November 2016,
Accepted 13th March 2017

DOI: 10.1039/c6cc09215b

rsc.li/chemcomm

1,2-Difunctionalization-type (hetero)arylation of unactivated alkenes triggered by radical addition/remote (hetero)aryl migration†

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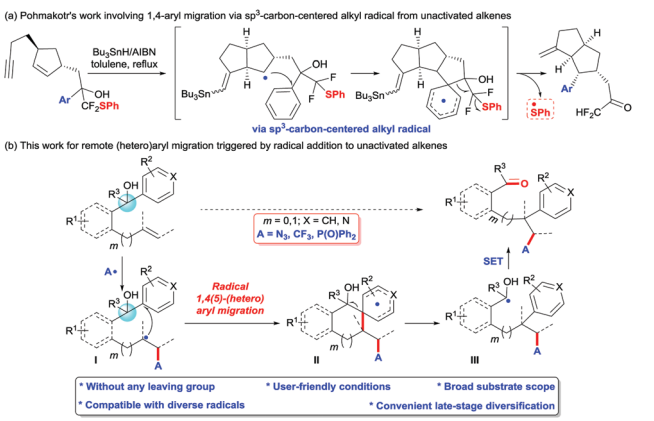
A novel difunctionalization-type (hetero)arylation of unactivated alkenes has been developed *via* remote 1,4(5)-(hetero)aryl migration triggered by radical alkene azidation, trifluoromethylation, or phosphonylation. The overall process serves as an unusual and reliable approach for straightforward access to diversely substituted ketones with broad functional group compatibility from readily available substrates and reagents.

The functionalization of unactivated alkenes triggered by intermolecular addition of a variety of radicals under mild conditions has emerged as a powerful tool for the preparation of complex organic molecules.[1] In particular, much effort has recently been devoted to the development of direct intermolecular radical difunctionalization-type arylation of unactivated alkenes involving simultaneous incorporation of arene and carbon- or heteroatom-centered radicals across C=C double bonds in one step.[2] On the other hand, an alternative approach leveraging a radical 1,2-aryl migration (neophyl rearrangement) initiated by the addition of radicals to allylic alcohols has been successfully developed[3] since the pioneering studies by the research groups of Tu,[3b] Wu,[3c] Sodeoka,[3d] and Zhu.[3e] Nevertheless, these developed methods are often limited to installation of one type of radical (trifluoromethyl-, alkyl-, phosphonyl-, or azido-radicals) or confined to allylic alcohol substrates for the generation of special α-aryl carbonyl ketones. Thus, their further application is significantly restricted.

More recently, we have reported an effective approach to realize remote α-C–H bond functionalization of amine *via* 1,5-hydrogen atom transfer (1,5-HAT) triggered by radical trifluoromethylation of alkenes.[4] Considering the fact that the bond-dissociation energy (BDE) of an α-C–H bond of amine is similar to that of a C–Ar bond of benzyl alcohol,[5] we anticipated the possibility of a remote aryl migration[6] elicited by inherently high-energy sp^3-carbon-centered alkyl radicals, such as radical **I**, which could be *in situ* generated from the addition of appropriate radicals to the unactivated alkenyl moiety of rationally designed substrates bearing benzyl alcohol at a remote position (Scheme 1b). Such a process is still relatively rare,[7] although considerable progress has been achieved on the difunctionalization of activated alkenes and alkynes involving a 1,4-aryl migration.[8] Of note, Pohmakotr has recently demonstrated elegant cascade radical cyclization/1,4-aryl migration of unactivated alkenes *via* a sp^3-carbon-centered alkyl radical intermediate, providing an efficient access to bicyclic rings (Scheme 1a).[7] However, this transformation requires the elimination of large phenyl-sulfanyl or -sulfonyl groups as the driving force in the presence of excess Bu_3SnH at high temperature.

Herein, we describe an efficient protocol for the successful implementation of radical reactions of alkenyl alcohols *via* an intramolecular remote 1,4(5)-(hetero)aryl migration triggered by radical azidation,[9] trifluoromethylation,[1] or phosphonylation[10] of unactivated alkenes in a highly controlled site-selective manner. These reactions do not require any leaving groups as the driving force, particularly proceed under mild and user-friendly conditions



Scheme 1 Remote (hetero)aryl migration triggered by radical addition to unactivated alkenes.

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† Electronic supplementary information (ESI) available: NMR, HRMS (ESI) and IR data are included. See DOI: 10.1039/c6cc09215b

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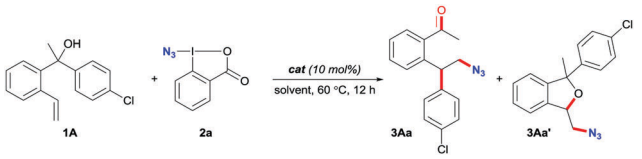
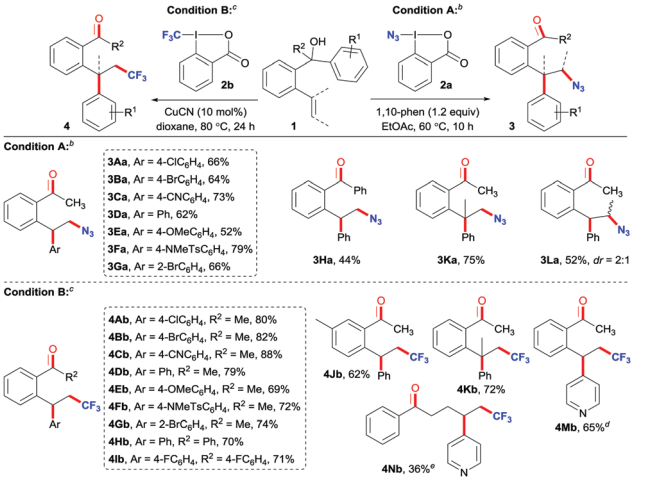
Table 1 Screening of reaction conditions for azidation reactions[a]



Entry	Catalyst	Solvent	Yield[b] (%) 3Aa	3Aa′
1	CuI	EtOAc	14	37
2	CuCl	EtOAc	27	11
3	CuBr	EtOAc	22	23
4	$Cu(CH_3CN)_4BF_4$	EtOAc	27	27
5	CuCN	EtOAc	54	2
6	CuCN	DCE	53	6
7	CuCN	DCM	50	12
8	CuCN	CH_3CN	12	40
9	CuCN	MeOH	28	5
10	$NaHCO_3$[c]	EtOAc	48	4
11	1,10-Phen[c]	EtOAc	66	—

[a] Reaction conditions: **1A** (0.3 mmol), **2a** (0.36 mmol), catalyst (10 mol%), solvent (3 mL). [b] Determined by ^{1}H-NMR spectroscopy with dibromomethane as an internal standard. [c] 1.2 equiv. was used. 1,10-phen = 1,10-phenanthroline.

Table 2 Substrate scope of azidation and trifluoromethylation reactions involving 1,4-(hetero)aryl migration[a]



[a] Isolated yield. [b] Condition A: **1** (0.3 mmol), **2a** (0.36 mmol), 1,10-phen (1.2 equiv.), EtOAc, 60 °C, 10 h. [c] Condition B: **1** (0.2 mmol), **2b** (0.4 mmol), CuCN (10 mol%), dioxane, 80 °C, 24 h. [d] CF_3CO_2H (1.2 equiv.) was added. [e] 80% conversion.

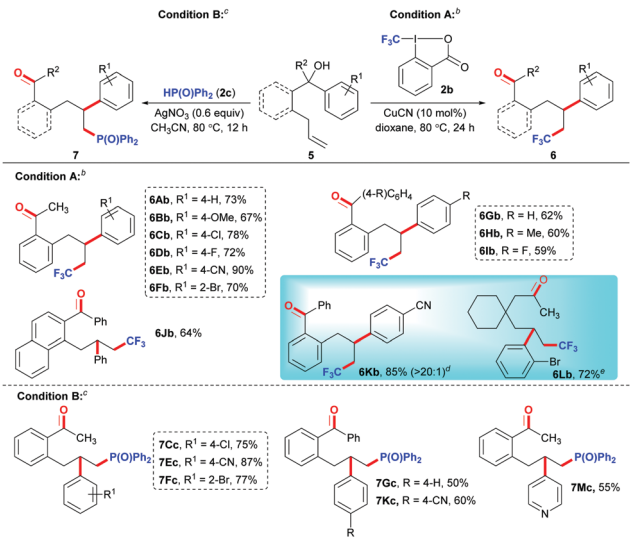
(Scheme 1b), and thus are advantageous compared to Pohmakotr's ones.[7] Notably, this protocol provides an unusual and reliable approach to the difunctionalization-type (hetero)arylation of unactivated alkenes with concomitant formation of carbonyl moieties at the remote position with remarkable precision and excellent functional group tolerance. In addition, the functional groups introduced during the transformation can serve as versatile handles for further transformations.

To validate our hypothesis, we initially investigated the reaction of alkenyl alcohol **1A** with the iodine(III) reagent azidoiodinane **2a** (Table 1),[11] considering that the development of methods for the incorporation of an azide moiety into organic compounds has enormous significance in chemistry, medicine, biology, and materials sciences.[12] We found that the desired product was indeed formed albeit in 14% yield together with a significant undesired 1,2-oxyazidation product in 37% yield when the simple CuI salt was used as a catalyst (Table 1, entry 1). To improve the efficiency of the process and to circumvent the 1,2-oxyazidation reaction, we further carried out systematic optimization of different reaction parameters through the variation of copper salts, additives, and solvents (Table 1, entries 2–11). We were delighted to find that the use of CuCN as the catalyst in EtOAc resulted in a significantly increased yield of 54% along with a trace amount of the 1,2-oxyazidation product (Table 1, entry 5). It is worth noting that the reaction proceeded well in the presence of 1,10-phen (1.2 equiv.) to give the product **3Aa** exclusively in 66% yield (Table 1, entry 11).[8c]

Given the optimal reaction conditions, we next set out to evaluate the substrate scope of the azidation reaction of alkenyl alcohols involving radical 1,4-aryl migration. As shown in Table 2, a range of substrates **1** bearing electron-neutral, -donating, or -withdrawing groups at the *para*- or *ortho*-position of the migrating aryl ring were tested and the desired migration products **3Aa–3Ga** were afforded in 52–79% yields. The alkenyl α,α-diaryl benzylic alcohol **1H** was tolerated to produce azido-substituted ketone **3Ha** in 44% yield. Moreover, substrate **1K** with a geminal-disubstituted alkenyl group was also well applicable to give **3Ka** containing a quaternary carbon center in 75% yield. Strikingly, even the internal alkenyl substrate **1L** was found to be compatible with our conditions to efficiently deliver diastereomers of **3La**, albeit in low stereoselectivity.

We then turned our attention to the 1,2-trifluoromethylarylation *via* radical 1,4-aryl migration triggered by radical trifluoromethylation of alkenes,[1] considering the increasing importance of trifluoromethylated organic molecules in agrochemicals, pharmaceuticals, and materials.[13] To our delight, after some optimization efforts including the evaluation of different copper catalysts, CF_3 reagents, molar ratios of the reactants, solvents, and reaction temperatures (Table S1 in ESI†), we found that the reaction of **1A** with Togni's reagent[14] **2b** (2.0 equiv.) proceeded smoothly using CuCN (10 mol%) as a catalyst in EtOAc at 80 °C for 24 h, giving the desired product **4Ab** in 80% yield with high chemoselectivity (Table 2, condition B). Both α-aryl-α-methyl- and α,α-diaryl-substituted benzyl alcohols bearing an electron-rich or -deficient group at different positions of the migrating aryl ring were found to be suitable substrates to give the corresponding products **4Ab–4Ib** selectively in 69–88% yields. Meanwhile, substrate **1J** with a 4-methylphenyl backbone reacted smoothly to afford **4Jb** in 62% yield. Most importantly, substrates **1K** and **1M** with a geminal-disubstituted alkenyl group or a heteroaryl pyridyl ring also underwent the migration process to furnish the desired products **4Kb** and **4Mb** in 72% and 65% yields, respectively. Besides, substrate **1N** without a fused phenyl ring in the backbone selectively underwent pyridine ring migration instead of a phenyl ring to afford product **4Nb**, albeit in low yield.

Table 3 Substrate scope of trifluoromethylation and phosphonylation reactions involving 1,5-(hetero)aryl migration[a]



[a] Isolated yield. [b] Condition A: **5** (0.2 mmol), **2b** (0.4 mmol), CuCN (10 mol%), dioxane, 80 °C, 24 h. [c] Condition B: **5** (0.2 mmol), **2c** (0.4 mmol), $AgNO_3$ (0.6 equiv.), CH_3CN, 80 °C, 12 h. [d] The ratio of **6Kb** to its isomer was determined by ^1H NMR analysis of the crude product. [e] EtOAc was used as a solvent.

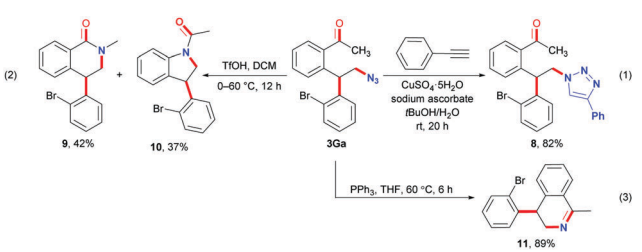
Encouraged by the above success in the radical 1,4-(hetero)-aryl migration process, we thus switched to the use of allylbenzene derivatives with one-carbon longer chains as substrates to probe whether a similar radical 1,5-aryl migration could be realized under the current reaction system (Table 3). Gratifyingly, the optimal trifluoromethylation reaction conditions for the 1,4-aryl migration process also worked best for readily available alkenyl alcohol **5A** (Table S2 in the ESI†). Under these conditions a broad range of substituents on the migrating aryl ring with diverse electronic properties and a naphthylidene-tethering group were all well tolerated to afford the corresponding products **6Ab–6Jb** in 59–90% yields. To investigate the selectivity of the aryl migration, we subjected unsymmetrically α,α-diaryl-substituted alkenyl alcohol **5K** to the standard conditions and found that only product **6Kb** *via* the migration of the electron-deficient *para*-cyano-substituted phenyl group was formed in 85% yield. This result indicates that the 1,5-aryl migration should involve a radical rather than a cationic intermediate.[6,15] Particularly noteworthy is that the current method could be extended to the aliphatic cyclohexylidene-tethered substrate **5L**. Under the standard reaction conditions, aliphatic ketone **6Lb** was obtained in 72% yield, indicating that the reaction was not significantly affected by switching multiply α-aryl-substituted alcohols to the singly α-aryl-substituted one.

Next, an *in situ* generated phosphonyl radical was also selected to probe whether a similar radical process could be realized, since phosphorus-containing compounds have wide applications in organic, medicinal, and material chemistries.[16] To our delight, the reaction of substrate **5C** with 2.0 equiv. of $Ph_2P(O)H$ (**2c**) in the presence of 0.6 equiv. of $AgNO_3$ in CH_3CN at 80 °C afforded the corresponding phosphonylated ketone **7Cc** in 75% yield (Table 3) after systematic optimization of different reaction parameters (Table S3 in the ESI†). Furthermore, a variety of α-(hetero)aryl-α-methyl- and α,α-diaryl-substituted benzylic alcohols bearing diversely substituted migrating aryl or pyridyl rings reacted smoothly with **2c**, affording the expected products **7Cc–7Mc** in good yields.

To gain some insights into the reaction mechanism, control experiments in the presence of several common radical scavengers were conducted to reveal significant inhibiting effects (eqn (1)–(3), Scheme S1 in the ESI†). In addition, no aryl scrambling was observed in products during the cross experiment between **1A** and **1J**, indicating an intramolecular aryl shift process (eqn (4), Scheme S1 in the ESI†). All these experimental results, together with the observed preferential migratory aptitude of an electron-deficient aryl group over an electron-neutral one, are in support of our initial proposal shown in Scheme 1b, in which the addition of a variety of *in situ* generated radicals to unactivated alkenes triggers the remote radical 1,4- or 1,5-(hetero)aryl migration process.

Further versatile transformation of the resultant compounds containing different valuable functional groups was subsequently investigated. **3Ga** with an azide group underwent a Huisgen cycloaddition reaction with phenyl acetylene by employing a copper(I) catalyst to give the corresponding triazole **8** in 82% yield (eqn (1) in Scheme 2). Interestingly, the intramolecular Schmidt–Aubé reaction of **3Ga** in the presence of trifluoromethanesulfonic acid (TfOH) was successfully realized to afford valuable bicyclic lactam **9** and indoline derivative **10** in 42% and 37% yields, respectively (eqn (2)). The PPh_3-promoted intramolecular Staudinger/aza-Wittig reaction[17] of **3Ga** generated dihydroisoquinoline **11** in 89% yield (eqn (3)).

In summary, we have successfully developed a novel and efficient difunctionalization-type (hetero)arylation of unactivated alkenes *via* intramolecular remote 1,4(5)-(hetero)aryl migration triggered by radical azidation, trifluoromethylation, or phosphonylation of alkenes under mild and user-friendly conditions. The overall process serves as an unusual and reliable approach for the construction of diversely substituted azido-, trifluoromethyl-, and phosphonyl-substituted ketones with good efficiency, remarkable selectivity and wide functional group compatibility from readily available substrates and reagents. The obtained products have been efficiently transformed into useful building blocks, such as lactam, indoline, triazole, and isoquinoline, demonstrating the high synthetic utility of the current process in organic and medicinal chemistry. Further investigation toward the catalytic asymmetric version of this reaction and the application of this



Scheme 2 Representative product transformations.

strategy to other substrate classes are currently ongoing in our laboratory.

Financial support from the National Natural Science Foundation of China (No. 21572096 and 21302088), the Shenzhen overseas high level talents innovation plan of technical innovation project (KQCX20150331101823702), and the Shenzhen special funds for the development of biomedicine, internet, new energy, and new material industries (JCYJ20150430160022517) is greatly appreciated.

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