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Palladium-Catalyzed Oxidative Heck-Type Alkylation/Aryl Migration/Desulfonylation between Alkenes with α-Carbonyl Alkyl Bromides

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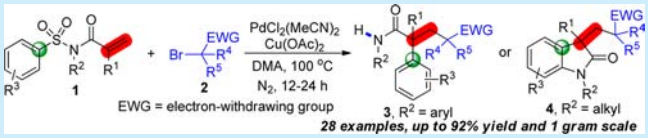
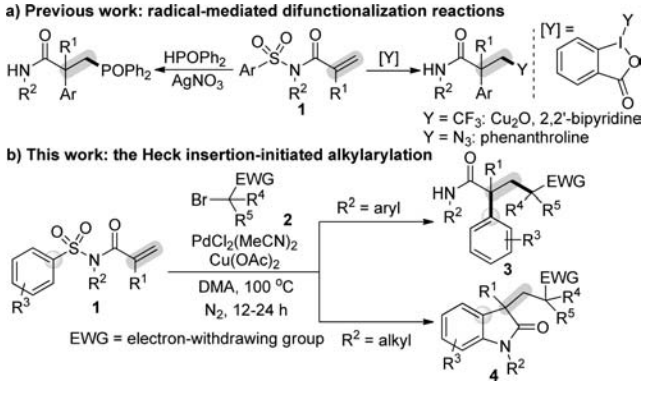
Supporting Information

ABSTRACT: A new Pd(II)-catalyzed alkene oxidative difunctionalization initiated by Heck insertion has been developed for the selective synthesis of acyclic and cyclic all-carbon quaternary stereocenters, which achieves an oxidative Heck-type alkylation, aryl migration, and desulfonylation sequence and represents a different input from those previously used Heck coupling in synthesis is reported.



All-carbon quaternary stereocenters are important key structural components that are found ubiquitously in biologically and pharmaceutically active molecules.[1] Therefore, their construction remains an active research area in synthesis.[1−4] The difunctionalization of alkenes is among the facile methods to build all-carbon quaternary stereocenters and has attracted much attention from synthetic chemists.[2−4] In this field, the carbofunctionalization process by the incorporation of an arene across an alkene recently provided significant breakthroughs for the all-carbon quaternary stereocenter synthesis.[3,4] However, the majority of these transformations proceed through arene intramolecular incorporation and are therefore limited to the construction of the cyclic quaternary stereocenters.[3] Recently, Novado and co-workers first reported an arene-migration incorporation strategy to build acyclic all-carbon quaternary stereocenters by Cu-catalyzed aryltrifluoromethylation of conjugated tosyl amides with Togni's reagent through an aryl-migration process (Scheme 1a).[4a,b] Subsequently, a similar strategy has been extended to arylphosphonylation and arylazidation of alkenes for accessing various acyclic quaternary stereocenters (Scheme 1a).[4c]

Scheme 1. Difunctionalization of Alkenes



Herein, we report a new type of arene incorporation strategy initiated by the oxidative Heck-type insertion, thus enabling the versatile assembly of acyclic all-carbon quaternary stereocenters from activated alkenes and a wide range of α-carbonyl alkyl bromides, including tertiary and secondary α-bromoalkyl esters, amides, and ketones (Scheme 1b); this method achieves the Heck-type alkylation, 1,4-aryl migration, and desulfonylation cascade by using $PdCl_2(MeCN)_2$ catalyst and $Cu(OAc)_2$ oxidant/cocatalyst and serves as a new example of alkene oxidative difunctionalization triggered by the Heck insertion. Notably, the chemoselectivity toward acyclic or cyclic quaternary stereocenters can be controlled by varying the substitution effect of the nitrogen atom.

Over the past several years transition-metal-catalyzed difunctionalization of alkenes with organohalides[5,6] or organometallic reagents[7] involving the Heck insertion[8] has proven to be a reliable tool to obtain diverse difunctionalized products, which often employs Pd catalysts to form a σ-alkyl palladium(II) intermediate via the Heck-type insertion into an alkene and then interception with another functional reagent.[5−7] Despite their importance, few methods initiated by the Heck insertion and especially under oxidative conditions[6,7] have been reported, and most are restricted to the formation of σ-alkyl palladium(II) intermediates from aryl halides[5] or arylmetallic reagents.[7] Only one paper on the σ-alkyl palladium(II) intermediate-forming from alkyl halides for alkene difunctionalization through the oxidative Heck insertion has been described.[6] However, this method is also limited to arene intramolecular incorporation leading to the cyclic quaternary stereocenters. Thus, a new oxidative Heck insertion-initiated arene incorporation strategy for alkene difunctionalization is desirable.

We initiated our study on the difunctionalization of *N*-phenyl-*N*-(phenylsulfonyl)methacrylamide (**1a**) with ethyl 2-bromo-2-methylpropanoate (**2a**) for reaction condition optimization

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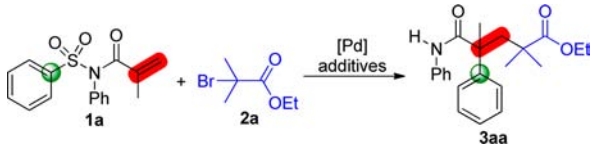
(Table 1).[9] In the presence of $PdCl_2(MeCN)_2$, Ag_2CO_3, and dppe, the previously reported efficient catalytic system,[6]

Table 1. Screening of Optimal Conditions[a]



entry	[Pd] (mol %)	additive (equiv)	yield (%)
1[b]	$PdCl_2(MeCN)_2$ (10)	Ag_2CO_3 (2)	43
2	$PdCl_2(MeCN)_2$ (10)	Ag_2CO_3 (2)	51
3	$PdCl_2(MeCN)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	72
4	$PdCl_2(MeCN)_2$ (10)	NaOAc (2)	trace
5	$PdCl_2(MeCN)_2$ (10)	*t*-BuOK (2)	trace
6	$PdCl_2(MeCN)_2$ (10)		6
7	$PdCl_2(MeCN)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (1)	32
8	$PdCl_2(MeCN)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (3)	71
9	$PdCl_2(MeCN)_2$ (15)	$Cu(OAc)_2{\cdot}H_2O$ (2)	70
10	$PdCl_2(MeCN)_2$ (7.5)	$Cu(OAc)_2{\cdot}H_2O$ (2)	65
11	$PdCl_2(MeCN)_2$ (5)	$Cu(OAc)_2{\cdot}H_2O$ (2)	20
12		$Cu(OAc)_2{\cdot}H_2O$ (2)	0
13	$PdCl_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	61
14	$PdCl_2(PPh_3)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	69
15	$Pd(dba)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	29
16[c]	$PdCl_2(MeCN)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	73

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), [Pd], additive, and DMA (*N*,*N*-dimethylacetamide; 2 mL) at 100 °C under N_2 atmosphere for 12 h. [b]Dppe (20 mol %). [c]Compound **1a** (1 g; 3.32 mmol) and DMA (10 mL) for 36 h.

acrylamide **1a** successfully underwent the Heck-type alkylation/aryl migration/desulfonylation sequence with alkyl bromide **2a**, giving the desired quaternary stereocenter **3aa** in 43% yield (entry 1). The results indicated that dppe ligand was not necessary, and its absence slightly increased the yield (51% yield; entry 2). Interestingly, inspired by these results, a series of other additives, including $Cu(OAc)_2$, NaOAc, and *t*-BuOK, were examined (entries 3−5). $Cu(OAc)_2$ showed higher reactivity than Ag_2CO_3 and furnished **3aa** in 72% yield (entry 3). However, the other additives, NaOAc and *t*-BuOK, had no effect on the reaction (entries 4 and 5). Notably, only 6% yield of **3aa** was isolated without additives (entry 6). These results suggest that $Cu(OAc)_2$ or Ag_2CO_3 may play as an oxidant and a cocatalyst. Among the amount of $Cu(OAc)_2$ examined, 2 equiv $Cu(OAc)_2$ was preferred (entry 3 vs entries 7 and 8). Screening on the amount of $PdCl_2(MeCN)_2$ revealed that 10 mol % of Pd was perfect (entries 3 and 9−11): yields similar to those of 10 mol % of Pd were achieved with 15 mol % of Pd, whereas the yield decreased to 65% when 7.5 mol % of Pd was used and to 20% with 5 mol % of Pd. However, no reaction was observed without Pd catalyst (entry 12). Three other Pd catalysts, namely $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(dba)_2$, also showed catalytic activity for the reaction (entries 13−15), but they were less efficient than $PdCl_2(MeCN)_2$. To our delight, the difunctionalization reaction of acrylamide **1a** was amenable to gram scale (entry 16).

Having determined the optimal reaction conditions for the assembly of quaternary stereocenter **3aa** in good yield,[9] we next investigated the scope of this Pd-catalyzed difunctionalization protocol with respect to *N*-(arylsulfonyl)acrylamides **1** (Figure 1 and Scheme 2) and *α*-carbonyl alkyl bromides **2** (Figure 2). As shown in Figure 1, a range of *N*-(arylsulfonyl)methacrylamides

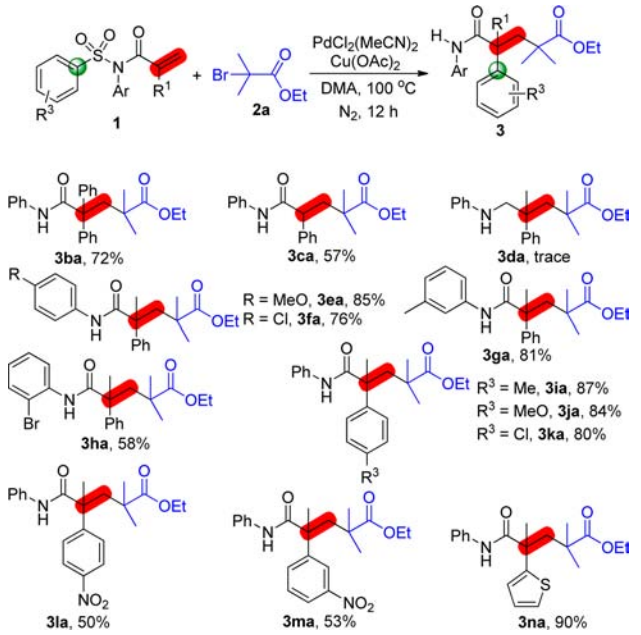
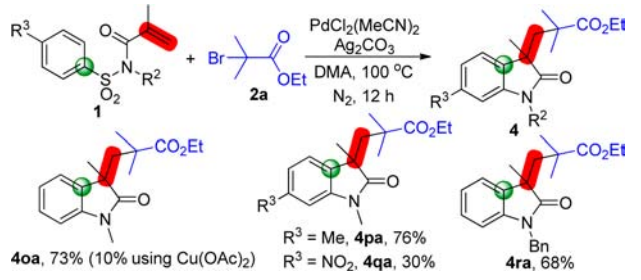


Figure 1. Variation of the *N*-aryl-*N*-(arylsulfonyl)acrylamides (**1**). Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $PdCl_2(CN)_2$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.6 mmol), and DMA (2 mL) at 100 °C under N_2 atmosphere for 12 h.

Scheme 2. Variation of the *N*-Alkyl-*N*-(arylsulfonyl)acrylamides (1)



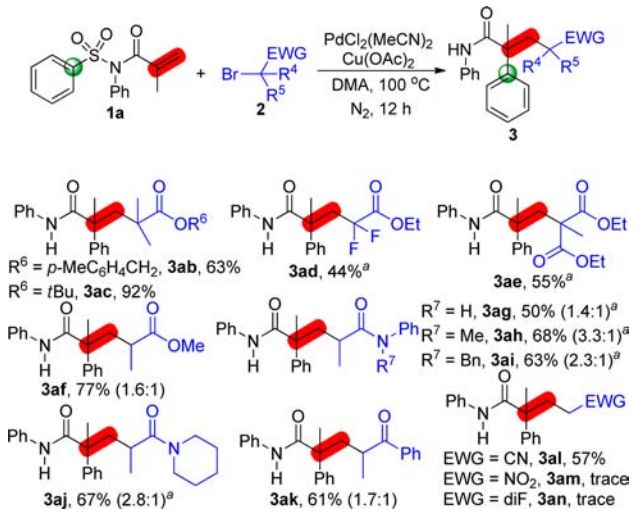


Figure 2. Variation of the *α*-carbonyl alkyl bromides (**2**). Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $PdCl_2(CN)_2$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.6 mmol), and DMA (2 mL) at 100 °C under N_2 atmosphere for 12 h. The dr value is given in parentheses determined by ^1H NMR analysis of the crude product **3**. [a]For 24 h.

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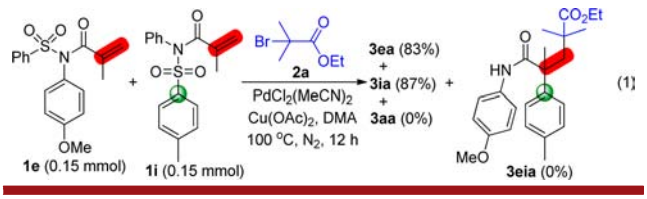
(**1**) bearing different substitution patterns were first examined in the presence of alkyl bromide **2a**, $PdCl_2(MeCN)_2$,and $Cu(OAc)_2$. Acrylamide **1b**, having a Ph group at the 2-position of the acrylamide moiety, successfully delivered diphenyl-substituted quaternary stereocenter **3ba** in 72% yield. Acrylamide **1c**, a monosubstituted alkene, was also a viable substrate for building **3ca** in 57% yield. However, an unactivated allylamine **1d** had no reactivity for the reaction (**3da**). A series of substituted aryl groups, including 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-MeC_6H_4, and 2-BrC_6H_4, on the nitrogen atom were compatible with the optimal conditions, although the substitution position has a strong influence on the yield. For example, *N*-4-ClC_6H_4-substituted acrylamide **1f** was converted into **3fa** in 76% yield, whereas *N*-2-BrC_6H_4-substituted acrylamide **1h** furnished **3ha** in only 58% yield. Screening on the substitution effect of the *N*-(arylsulfonyl) moiety revealed that several substituents, such as Me, MeO, Cl, and NO_2, on the aromatic ring were well-tolerated, giving **3ia**−**ma** in moderate to excellent yields. Additionally, the electronic properties of the substituents affected the reaction, and the reactivity order is as follow: electron-donating groups (Me or MeO) > electron-withdrawing groups (Cl or NO_2). It is noteworthy that halide motifs are accommodated by the optimal conditions and provide further opportunities for additional modifications of the quaternary stereocenter (**3fa**, **3ha**, and **3ka**). Gratifyingly, acrylamide **1n** with a *N*-(thiophene-2-ylsulfonyl) group also had high reactivity to form **3na** in 90% yield.

As shown in Scheme 2, acrylamides **1o**−**r**, bearing an alkyl group on the nitrogen atom, offered cyclic quaternary stereocenters (oxindoles) **4oa**−**ra**, not the desired acyclic quaternary stereocenters. For example, *N*-methyl-substituted acrylamide **1o** underwent the reaction with alkyl bromide **2a**, $PdCl_2(MeCN)_2$, and Ag_2CO_3 smoothly, providing **4oa** in 73% yield. However, using $Cu(OAc)_2$ instead of Ag_2CO_3 decreased the yield to 10%. The other *N*-Me-substituted acrylamides **1p** and **1q** successfully delivered **4pa** and **4qa** in 76% and 30% yields, respectively. The regioselectivity of **4pa** and **4qa** suggests that the addition of aryl group across alkene selectively occurs at the *ipso*-carbon atom of the aryl C(sp^2)−S bond. Interestingly, acrylamide **1r** with a *N*-Bn group is suitable for assembling **4ra** in 68% yield.

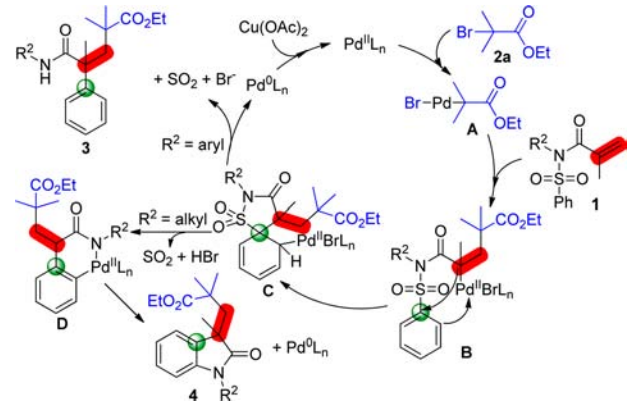
We next apply the optimal conditions for the reaction of acrylamide **1a** with various α-carbonyl alkyl bromides **2b**−**n** (Figure 2). Bromides **2b** and **2c** with a *N*-*p*-methylbenzyl or a *N*-*tert*-butyl group were effective substrates for building **3ab** and **3ac** in 63% and 92% yields, respectively. It should be noted that the optimal conditions are feasible with ethyl 2-bromo-2,2-difluoroacetate (**2d**) leading to a difluoro-containing quaternary stereocenter **3ad**, albeit giving a lower yield. Using diethyl 2-bromo-2-methylmalonate (**2e**), product **3ae** was successfully constructed in 55% yield. Gratifyingly, the optimal conditions were applicable to diverse secondary α-carbonyl alkyl bromides, including ester **2f**, amides **2g**−**j**, and ketone **2k**, and primary bromide **2l** (**3af**−**al**) However, bromo(nitro)methane (**2m**) and bromodifluoromethane (**2n**) had no reactivity (**3am** and **3an**).

To understand the mechanism of the current protocol, a mixture of acrylamides **1e** and **1i** was employed to react with bromide **2a** (eq 1): no crossover products **3aa** and **3eia** were observed, implying that the reaction occurs via an intramolecular aryl-migration process.

Consequently, the possible mechanisms outlined in Scheme 3 were proposed.[1,4,6−8] Initially, insertion of the active $Pd^{II}L_n$ species into the C−Br bond of **2a** affords intermediate **A**, followed by addition across alkene **1** produces intermediate **B**.[6−8] *ipso*-Cyclization of intermediate **B** occurs to give a spiro-



Scheme 3. Possible Mechanisms



intermediate **C**.[1,4] Intermediate **C** undergoes desulfonylation to selectively form a N−H bond or a C(sp^2)−N bond, which is affected by the N-substitution effect.[4] While *N*-aryl-substituted intermediate **C** directly undergoes reductive elimination leading to the acyclic quaternary stereocenter **3**, the *N*-alkyl-contained intermediate **C** assembles the cyclic quaternary stereocenter **4** because the nitrogen atom with an alkyl group is more nucleophilic and constructs a N−Pd bond (intermediate **D**), thus forming a C(sp^2)−N bond by reductive elimination.

In summary, a new type of alkene oxidative difunctionalization initiated by Heck insertion for the selective synthesis of acylic and cyclic quaternary stereocenters has been developed and proceeds by arene-migration incorporation. The method is triggered by the Pd(II)-catalyzed oxidative Heck-type coupling between alkenes and challenging secondary/tertiary α-carbonyl alkyl bromides with subsequent 1,4-aryl migration and desulfonylation, which is amenable to a range of functional groups with good levels of chemoselectivity control.

■ ASSOCIATED CONTENT

Supporting Information

Descriptions of experimental procedures for compounds and analytical characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) The detailed data of the optimal conditions (Table S1) are summarized in the Supporting Information.

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