JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Copper-Catalyzed Enantioselective Intramolecular Alkene Amination/Intermolecular Heck-Type Coupling Cascade

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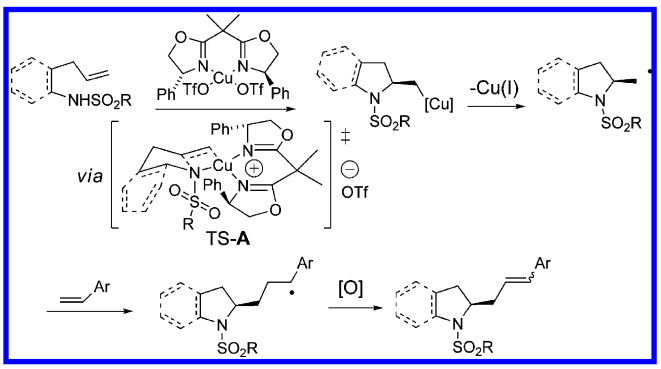
Supporting Information

ABSTRACT: Enantioselective copper-catalyzed cyclization of γ-alkenylsulfonamides and a δ-alkenylsulfonamide in the presence of a range of vinyl arenes results in variously functionalized 2-substituted chiral nitrogen heterocycles via a formal alkene C−H functionalization process. Application of this reaction to the concise synthesis of a 5-HT_7 receptor antagonist is demonstrated.

The C−H functionalization of alkenes is currently under intensive study as a direct carbon−carbon bond-forming method for the synthesis of higher substituted alkenes.[1] The commonly employed Heck reaction[2] enables direct C−H to C−C functionalization of alkenes with aryl and vinylhalides, but is rarely performed[3] with alkyl halide coupling partners due to the propensity of the alkyl to undergo β-hydride elimination. The Heck-type coupling with alkyl halides has experienced some success with alternative methods that involve carbon radical intermediates, generally of low functionality.[3b,4] New methods for the oxidative coupling of more functionalized alkyl groups with alkenes, however, are still required. Along these lines, the intermolecular oxidative Heck-type coupling of β-amino alkyl reagents with alkenes is unprecedented.[5] Herein is reported the first intermolecular oxidative Heck-type coupling with a β-aminoalkyl intermediate.[6] Furthermore, rather than starting from a preformed chiral β-amino alkyl halide, we envisioned the alkene could intercept a chiral β-aminoalkyl radical generated *in situ* from an enantioselective aminocupration of a γ-aminoalkene followed by C−Cu(II) homolysis. Under oxidizing reaction conditions, the resulting carbon radical coupling intermediate could be oxidized to an alkene, thus completing a net Heck-type reaction sequence (Scheme 1).

Scheme 1. Alkene Amination−Heck-Type Coupling Cascade



We have previously shown that γ-pentenylsulfonamides undergo enantioselective Cu-catalyzed aminofunctionalizations, for example, carboamination,[7] aminooxygenation,[8] and diamination.[9] These reactions involve carbon radical intermediates as evidenced by radical trapping experiments and regio- and stereoselectivity patterns of reactivity.[10] The particular aminofunctionalization observed is a function of substrate structure and reaction components.[11] The reaction disclosed herein significantly extends our previously reported doubly intramolecular carboamination methodology[7] to an intermolecular C−C bond-forming process by using aryl-substituted alkenes as the otherwise unfunctionalized π-component.[12] The resulting allyl-functionalized chiral indoline, pyrrolidine, and tetrahydroisoquinoline products (*vide infra*) should find application in drug discovery and organic synthesis.

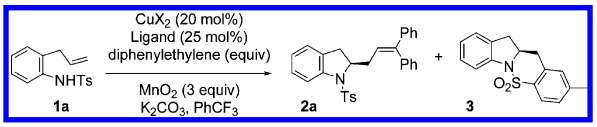
The intermolecular carboamination reaction was first investigated with *N*-tosyl-2-allylaniline **1a** using 1,1-diphenylethylene (DPE) as the aryl alkene coupling partner.[13] At the onset, we were uncertain if intermolecular radical addition to DPE would out-compete an intramolecular carboamination process, where the radical adds to the aryl ring of the tosyl group, generating sultam **3**.[7a] While the reaction promoted by Cu(2-ethylhexanoate)$_2$, a copper(II) source known to promote the alkene amination step,[11] provided a low yield of **2a** (Table 1, entry 1), the catalytic version, using Cu(OTf)$_2$ (20 mol%), the 2,2′-bipyridine ligand, and MnO_2 (3 equiv) as the stoichiometric oxidant provided a higher yield of **2a** (Table 1, entry 2). Encouraged by these results, we further employed (*R*,*R*)-Ph-box as the ligand to enable an enantioselective variant. To our delight, this process was feasible, and chiral indoline **2a** was formed in 62% yield and 73% ee (Table 1, entry 3). We found that use of activated 4 Å molecular sieves was beneficial to the yield and enantioselectivity (Table 1, entry 4). While an increase in diphenylethylene equivalents and reaction concentration did not further increase the yield of **2a**, the DPE stoichiometry could be reduced to 3 equiv (Table 1, entries 5−7). The yield of **2a** peaked around 75%, where the remaining mass was predominantly sultam **3** (15%). We further optimized the reaction by reducing reaction temperature and time (Table 1, entry 8). The catalyst loading could also be further reduced to 15 mol % Cu(OTf)$_2$ for this substrate (Table 1, entry 9).

Following the optimized conditions (Table 1, entry 8), a series of substituted *N*-sulfonyl-2-allylanilines underwent the enantioselective alkene amination/Heck-type coupling reaction

Received: December 1, 2011
Published: January 17, 2012

dx.doi.org/10.1021/ja211272v | J. Am. Chem. Soc. 2012, 134, 2020−2023

Table 1. Alkene Amination–Heck-Type Coupling Optimization[a]



entry	CuX_2·ligand	DPE equiv	time (h), temp (°C)	yield[b] **2a** (**3**)	ee[c]
1[d,e]	$Cu(eh)_2$	5	24, 120	51 (40)	
2[e]	$Cu(OTf)_2$·Bipy	5	24, 120	65 (30)	
3[e]	$Cu(OTf)_2$·(*R,R*)-Ph-box	5	24, 120	62 (25)	73
4[e,f]	$Cu(OTf)_2$·(*R,R*)-Ph-box	5	24, 120	75 (15)	88
5[f,g]	$Cu(OTf)_2$·(*R,R*)-Ph-box	5	24, 120	76 (15)	87
6[f,g]	$Cu(OTf)_2$·(*R,R*)-Ph-box	8	24, 120	75 (15)	nd
7[f,g]	$Cu(OTf)_2$·(*R,R*)-Ph-box	3	24, 120	74 (15)	89
8[f,g]	$Cu(OTf)_2$·(*R,R*)-Ph-box	3	8, 105	75 (15)	92
9[f,g,h]	$Cu(OTf)_2$·(*R,R*)-Ph-box	3	8, 105	75 (15)	91

[a]Reactions run with **1a** (0.174 mmol), Cu(II) (0.0348 mmol), ligand (0.0435 mmol), DPE (equiv), K_2CO_3 (0.174 mmol), and MnO_2 (0.522 mmol) in CF_3Ph (0.15 M) unless otherwise noted. [b]Isolated yield after flash chromatography on SiO_2. [c]Determined by chiral HPLC analysis. [d]$Cu(eh)_2$ (3 equiv) used in this reaction. [e]Reaction run at 0.10 M with respect to **1a**. [f]Reaction carried out with activated 4 Å mol. sieves. [g]Reaction run at 0.15 M with respect to **1a**. [h]Reaction run with 15 mol% $Cu(OTf)_2$ and 19 mol% (*R,R*)-Ph-box. L = ligand, bipy = 2,2′-bipyridine, $Cu(eh)_2$ = copper (2-ethylhexanoate)$_2$, DPE = 1, 1-diphenylethylene. nd = not determined.

with vinylarenes. As illustrated in Table 2, the *N*-arylsulfonylanilines gave products with relatively higher enantiomeric excess than the *N*-mesyl- and *N*-trimethylsilylethylsulfonyl analogues (compare Table 2, entries 1–4 to entries 5 and 6). The yields and selectivities were relatively insensitive to the nature of the 4-substitution on the aniline (F, Cl, MeO, see Table 2, entries 7–9). Although diphenylethylene is generally the most reactive coupling partner, other vinylarenes such as styrene, α-methylstyrene, α-acetoxystyrene, α-pivaloxystyrene, benzofuran, and 3-methylbenzofuran also yielded coupling products. The coupling with styrene provided a mixture (4:1 *E:Z*) of alkene isomers (Table 2, entry 10). Ozonolysis of this mixture followed by reductive workup with $NaBH_4$ provided one terminal alcohol product in 88% ee (see Supporting Information for details). Coupling of **1a** with α-methylstyrene provided an inseparable 3:1 mixture of the internal and terminal alkenes, **2k** and **2l**, respectively (Table 2, entry 11). Ozonolysis of this mixture provided the respective aldehyde and ketone in 85% and 91% ee (see Supporting Information for details). The β-amino aldehyde derived from **2k** has a lower %ee, possibly due to configurational instability (via reversible retro-Michael/Michael addition). Coupling of **1a** with α-acetoxystyrene[4e] provided ketone **2m** in 82% ee, albeit in only 20% yield (Table 2, entry 12). The remainder of the material was *N*-acyl-*N*-tosyl-2-allylaniline along with sultam **3**. Changing to the α-pivaloxystyrene coupling partner provides **2m** in 50% yield and 90% ee.

Coupling of *N*-mesyl-2-allylaniline **1e** with benzofuran and 3-methylbenzofuran, respectively, provided the unique coupling products **2n** and **2o**, albeit is relatively lower %ee (Table 2, entries 14 and 15). In these reactions the *N*-tosyl substrate **1a** was less effective, and intramolecular carboamination product **3** predominated (not shown). A comparison of Table 2, entries 5, 14, and 15, also illustrates that the reactivity of the coupling partner can affect the enantioselectivity. This seems to indicate that if the coupling partner is not highly reactive toward radical addition, the alkyl radical intermediate could ring open and close reversibly prior to coupling, resulting in erosion of enantioselectivity. It is also noteworthy that *N*-tosyl-2-allylaniline **1a** gave the sultam **3** in low enantioselectivity in our doubly intramolecular carboamination reaction,[7a] while the majority of the intra-/intermolecular reactions in Table 2 provide indolines with very good %ee. This again seems to indicate that if the carbon radical addition is rapid, selectivity erosion via ring-opening becomes less problematic.

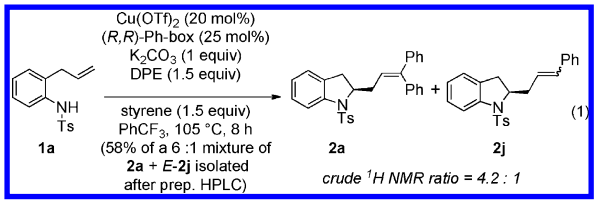
Electron-deficient alkene coupling partners such as acrylonitrile, methyl methacrylate, and 2(5*H*)-furanone either were not reactive, underwent aza-Michael addition (acrylonitrile), or produced what appeared to be polymers in reactions with **1a** or **1e**.

4-Pentenylsulfonamides **4** also underwent the coupling reaction in good yield and moderate to excellent enantioselectivity (Table 3). These relatively less reactive substrates required longer reaction time (24 h) and higher temperature (120 °C). It is instructive that both the carbon backbone and the *N*-sulfonyl group have a significant effect on the enantioselectivity. For example, the *N*-tosyl substrate **4a** provided the DPE coupling product **5a** in 92% ee, while the *N*-mesyl substrate **4b** gave **5b** in only 55% ee (Table 3, entries 1 and 2). The *N*-tosyl-2,2-diphenyl-4-pentene **4c** reacted with the highest enantioselectivity, 95% ee, while the *N*-mesyl-2,2-diphenyl-4-pentene **4d** provided the coupled product in 90% ee (Table 3, entries 3 and 4). Clearly the 2,2-diphenyl substitution has a significant affect on the enantioselectivity. An example of a six-membered ring synthesis is shown in Table 3, entry 7, where a chiral isoquinoline **7** is formed in 51% yield and 79% ee. This substrate was less reactive and required a 48 h reaction time. It is noteworthy that most of the coupling products are crystalline, so their enantiopurity can in principle be increased by recrystallization.

The absolute stereochemistry of **2a** was established by X-ray crystallography. The stereochemistry of **2b–2o**, **4a–4f**, and **6** was assigned by analogy to **2a** and literature precedent.[7,8]

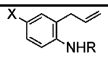
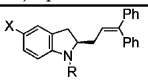
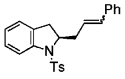
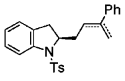
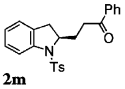
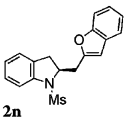
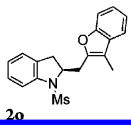
The proposed mechanism for this reaction is shown in Scheme 1. Ligand exchange provides the reactive R_2N-[Cu] complex. Stereodetermining *cis*-aminocupration occurs via chairlike transition state **A** that places the *N*-substituent anti to the closest bis(oxazoline) phenyl substituent. The resulting unstable organocopper(II) species undergoes homolysis to provide Cu(I) and the corresponding primary carbon radical. Radical addition to the vinylarene and subsequent oxidation of the resulting benzylic radical provides the chiral nitrogen heterocycle.

An alternative mechanism for addition to the vinylarene could involve carbocupration of the organocopper intermediate followed by β-hydride elimination.[2e–g] To differentiate between carbon radical addition and carbocupration for this step, a competition experiment was performed where indoline **1a** underwent the alkene amination/Heck-type cascade in the presence of 1.5 equiv of DPE and 1.5 equiv of styrene (eq 1).



dx.doi.org/10.1021/ja211272v | J. Am. Chem. Soc. 2012, 134, 2020–2023

Table 2. Indoline Synthesis Scope[a]

entry	substrate	alkene	major product	yield[b]	ee[c]
1	 **1a**, X = H, R = Ts	 (DPE)	 **2a**	75	91
2	**1b**, X = H, R = Bs	DPE	**2b**, X = H, R = Bs	85	88
3	**1c**, X = H, R = Ns	DPE	**2c**, X = H, R = Ns	65	87
4	**1d**, X = H, R = 3,5-di-*t*-Bu-$C_6H_3SO_2$	DPE	**2d**, X = H, R = 3,5-di-*t*-Bu$C_6H_3SO_2$	82	88
5	**1e**, X = H, R = Ms	DPE	**2e**, X = H, R = Ms	84	83
6	**1f**, X = H, R = SES	DPE	**2f**, X = H, R = SES	80	71
7	**1g**, X = F, R = Ts	DPE	**2g**, X = F, R = Ts	84	88
8	**1h**, X = OMe, R = Ts	DPE	**2h**, X = OMe, R = Ts	77	86
9	**1i**, X = Cl, R = Ts	DPE	**2i**, X = Cl, R = Ts	83	91
10	**1a**		 **2j** ($E:Z = 4:1$)	71	88
11	**1a**		 internal alkene **2k** /terminal alkene **2l** = 3 : 1)	73	85/91
12[d]	**1a**		 **2m**	20	82
13[d]	**1a**		**2m**	50	90
14[e,f]	**1e**		 **2n**	60	58
15[e]	**1e**		 **2o**	73	40

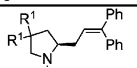
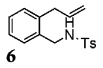
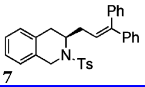
[a]The same conditions as Table 1, entry 8, were used in these reactions. These conditions were more general than Table 1, entry 9. Yields and ee's are the average of two runs. [b]Isolated yield. [c]Determined by chiral HPLC. [d]*N*-Acylation was a competing side reaction. [e]Reaction run at 120 °C for 24 h. [f]*N*-Mesyl-2-methylindoline, a hydroamination product, was a minor component of the crude mixture.

We reasoned that a radical mechanism should favor addition to DPE over styrene since radicals generally add more rapidly to DPE.[13] Conversely, in analogy to the migratory insertion step in the Pd-catalyzed Heck reaction, a carbocupration mechanism should favor addition to styrene, which is less hindered than DPE.[2d] (It is also noteworthy that styrene, but not diphenylethylene, is a substrate for Cu-catalyzed Heck reactions.[2e−g]) This competition reaction led to formation of a 4.2:1 mixture of **2a** and **2j** (eq 1). Thus, it appears the radical mechanism is more likely.

Scheme 1 shows the stereochemistry-determining step to be the *cis*-aminocupration, yet in Table 2 we observe that the nature of the vinyl arene can affect the enantioselectivity of the reaction (*vide supra*). This could be indicating that the organocopper intermediate or the carbon radical can undergo some degree of ring-opening and unselective re-closing if the vinylarene is not a very reactive radical acceptor.

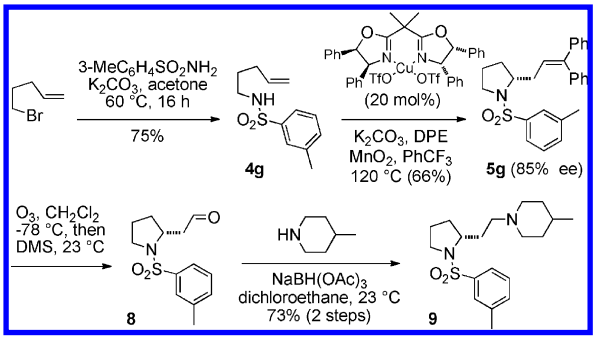
An illustration of the utility of this reaction is shown in the concise synthesis of a 5-HT_7 receptor antagonist **9** (Scheme 2).[14]

Table 3. Pyrrolidine and Tetrahydroisoquinoline Synthesis[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]
1	 **4a**, R^1 = Me, R^2 = Ts	 **5a**	74	92
2	**4b**, R^1 = Me, R^2 = Ms	**5b**, R^1 = Me, R^2 = Ms	88	55
3	**4c**, R^1 = Ph, R^2 = Ts	**5c**, R^1 = Ph, R^2 = Ts	68	95
4	**4d**, R^1 = Ph, R^2 = Ms	**5d**, R^1 = Ph, R^2 = Ms	68	90
5	**4e**, R^1 = H, R^2 = Ts	**5e**, R^1 = H, R^2 = Ts	62	80
6	**4f**, R^1 = H, R^2 =3,5-di-*t*-$BuC_6H_3SO_2$	**5f**, R^1 = H, R^2 =3,5-di-*t*-$BuC_6H_3SO_2$	88	nd[d]
7[e]	 **6**	 **7**	51	79

[a]The same general reaction conditions as Table 1, entry 8, were used except the reactions were run at 120 °C for 24 h. [b]Isolated yields from flash chromatography on SiO_2. [c]Enantiomeric excess determined by chiral HPLC analysis. [d]Not determined. The enantiomers could not be separated by chiral HPLC. [e]Reaction was run for 48 h.

Scheme 2. Concise Synthesis of a 5-HT_7 Receptor Antagonist



Synthesis of sulfonamide **4g** was performed by S_N2 displacement on the commercially available 5-bromo-1-pentene with 3-methylbenzenesulfonamide. The enantioselective amination/Heck-type cascade reaction provided pyrrolidine **5g** in 66% yield and 85% ee. The (4*S*,5*R*)-di-Ph-box ligand was used in this example because it provided greater enantioselectivity than (*S*,*S*)-Ph-box. Oxidative cleavage of the alkene and subsequent reductive amination provided

dx.doi.org/10.1021/ja211272v | *J. Am. Chem. Soc.* 2012, 134, 2020−2023

the 5-HT$_7$ receptor antagonist **9**. This synthesis was accomplished in 4 steps from commercially available reagents without the aid of protecting groups and is several steps shorter than its original synthesis.[14]

In conclusion, we have developed an efficient and enantioselective alkyl Heck-type coupling cascade for the formation of functionalized chiral indolines, pyrrolidines and an isoquinoline from the respective acyclic γ- and δ-alkenylsulfonamides. The concise synthesis of a 5-HT$_7$ receptor antagonist was accomplished to demonstrate the utility of the method. Sulfonamides and sultams are common moieties found in bioactive compounds.[14,15] This method accesses such targets directly, enantioselectively and without the use of protecting groups. Removal of the *N*-sulfonyl groups can further provide valuable chiral amines. Further investigation into the heterocycle and alkene scope and application in the total synthesis of bioactive alkaloids is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and crystallography data of **2a** (CIF). 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.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (NIGMS 078383) for support of this work. We thank William W. Brennessel and the X-ray Crystallographic Facility at the University of Rochester for the X-ray structure of **2a**.

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