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Copper-Catalyzed Cross-Coupling of Imines, Acid Chlorides, and Organostannanes: A Multicomponent Synthesis of α-Substituted Amides

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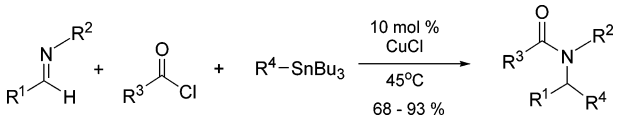

A copper-catalyzed cross-coupling of organotin reagents with imines and acid chlorides is reported. The reaction proceeds efficiently with a range of vinyl-, alkyl-, aryl- and heteroaryl-substituted organostannanes as well as a diverse set of imines of non-enolizable aldehydes. Use of chloroformates also allows for the formation of N-protected α-substituted amines. This chemistry has been applied to the synthesis of isoquinoline alkaloid derivatives through the activation of cyclic imines.

Introduction

The palladium-catalyzed cross-coupling of organic electrophiles with organostannanes, known as the Stille coupling, has received growing attention as a mild and selective method for carbon−carbon bond formation.[1] A useful feature of the Stille reaction is the diverse array of organotin reagents compatible with coupling, as well as their low intrinsic reactivity. This often allows the reaction of functionalized electrophiles and organotin reagents in late stages of complex molecule synthesis without prior functional group protection.[1a,2] In addition, Stille and related cross-couplings have been demonstrated to proceed efficiently with a range of R−X electrophiles. These include classic examples, such as organic-halides or -sulfonates,[1] as well as a wide range of more recently developed coupling partners (e.g., diazonium salts,[3] iodonium salts,[4] esters or carboxylic acid derivatives,[5,6] arylimidazoles,[7] ammonium salts,[8] etc.).

While Stille couplings have proven to be a straightforward approach to carbon−carbon bond formation with R−X substrates, a typical limitation of this reaction is its inability to mediate a similar coupling with multiply bonded electrophiles, such as imines. This results, in part, from the inability of these substrates to undergo what is presumably the first mechanistic step of cross coupling reactions: the direct addition to Pd(0) to form a Pd−C bond.[9] This limitation is of significance, since imines are readily modified building block for synthesis, and carbon−carbon bond formation with imines provides a route to prepare α-substituted amines or amides. The latter represent one of the most common core structures in biologically relevant molecules. The nucleophilic addition of organolithium, organozinc, or Grignard reagents to imines has been elegantly exploited as a route to prepare chiral α-substituted amines;[10] however, these reactions

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(4) (a) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997.

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(7) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421.

(8) (a) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, *14*, 975. (b) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

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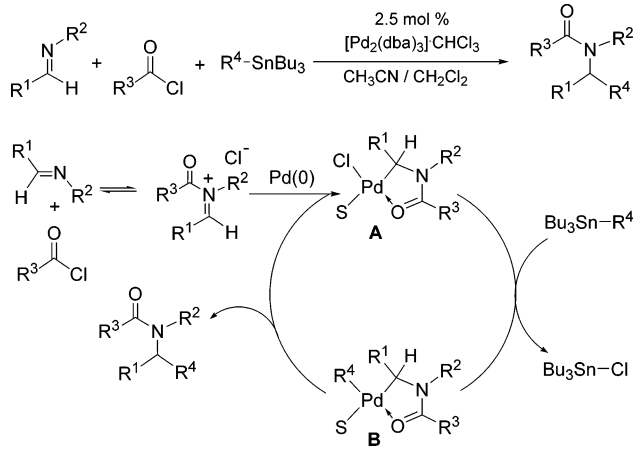
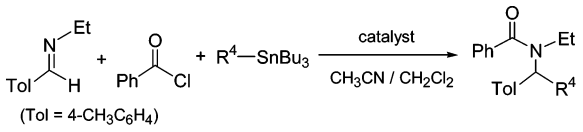
SCHEME 1. Palladium-Catalyzed Coupling of Imines, Acid Chlorides, and Organostannanes



are often less mild and functional group compatible than typical Stille couplings. Alternatively, non-imine-based palladium-catalyzed cross-coupling routes to α-substituted amines and amides have also been developed, such as the α-arylation or allylation of glycine derivatives.[11] In addition, the rhodium catalyzed reaction of organoboranes or organostannanes with imines allows for the formation of α-substituted amines through an alternative mechanism.[12]

We have recently demonstrated that while imines themselves are incompatible with palladium catalyzed Stille couplings with organotin reagents, they can be induced to undergo cross-coupling by the simple addition of acid chlorides (Scheme 1).[13] This presumably occurs via the acid chloride stabilization of imine oxidative addition to palladium as palladacycle **A**,[14] followed by transmetalation of the organotin reagent and reductive elimination. This provides a relatively mild cross-coupling method to employ imines for the synthesis of α-substituted amides. Nevertheless, our previous report was limited primarily to the use of vinyl-tin reagents as a coupling partner. As such, we have undertaken a study of the potential use of more diverse organostannanes in this three component coupling. This has led to the design of an efficient copper(I)-catalyzed multicomponent synthesis of a broad range of α-substituted amides and N-protected α-substituted amines, as is described below.

TABLE 1. Copper-Catalyzed Cross-Coupling with Imines



Entry	R^4	Catalyst	Temp.	Yield[a]
1[b]		2.5 % $Pd_2(dba)_3{\cdot}CHCl_3$	25°C	82%
2	Ph	2.5 % $Pd_2(dba)_3{\cdot}CHCl_3$	110°C	0%
3	Bn	2.5 % $Pd_2(dba)_3{\cdot}CHCl_3$	110°C	0%
4		2.5 % $Pd_2(dba)_3{\cdot}CHCl_3$	110°C	0%
5	Ph	2.5 % $Pd_2(dba)_3{\cdot}CHCl_3$ 10 % CuCl	45°C	88%
6	Ph	10 % CuCl	45°C	84%
7	Ph	10 % CuCl	65°C	10%[c]

[a] 0.48 mmol of imine, 0.63 mmol of acid chloride, 0.48 mmol of organotin reagent, and with the given catalysts in CH_3CN (4 mL) and CH_2Cl_2 (3 mL) for 26 h. [b] See ref 13. [c] 80% benzophenone isolated, due to coupling of the organostannane and the acid chloride.

Results and Discussion

Our initial attempts to employ non-vinyl substituted organotin reagents in the palladium catalyzed coupling with imine and acid chloride are outlined in Table 1. As can be seen, many of the other stannanes typically employed in Stille coupling (e.g., aryl-, heteroaryl-, and benzylstannanes) were unable to undergo this reaction. Although the reason for this is not clear, our working postulate is that steric interactions at the Pd center between the metal-chelated amide (intermediate **A**) and the organotin reagent may prevent the transmetalation of these less reactive substrates from occurring at an appreciable rate.[15] One potential approach that has been previously reported to accelerate transmetalation in Stille reactions involves the use of cocatalytic copper(I) salts.[1,16] The latter have been postulated to mediate the coupling through a reaction between the copper(I) center and the organostannane to form a transient organocuprate,[17] which can undergo a more rapid transmetalation to palladium than the organotin reagent itself. Indeed, the addition of 10 mol % of CuCl to the palladium catalyzed coupling led to complete disappearance of the starting materials over 26 h at 45 °C, and formation of the α-aryl substituted amide in 88% yield (Table 1, entry 5). Interestingly, however, when this same catalytic reaction with 10 mol % of CuCl is performed in the absence of Pd(0), the α-substituted amide product is also observed in 84% yield (entry 6).

(10) For reviews: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(11) (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (c) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (d) Genet, J. P.; Ferroud, D.; Juge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573. (e) Genet, J. P.; Juge, S.; Achi, S.; Mallart, S.; Ruiz Montes, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.

(12) (a) Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* **1999**, *40*, 9259. (b) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, *11*, 1637. (c) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(13) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 590.

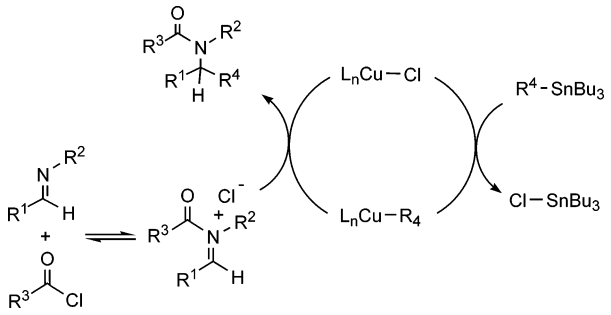
(14) (a) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634. (b) Lafrance, D.; Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Organometallics* **2001**, *20*, 1128. (c) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228. (d) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474.

(15) Even the more reactive Me_3Sn-Ph does not undergo cross-coupling with imines at temperatures up to 110 °C.

(16) (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (c) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408. (d) Satoh, T.; Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1994**, *13*, 4431. (e) Saá, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963.

(17) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (b) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305. (c) Wipf, P. *Synthesis* **1993**, *6*, 537.

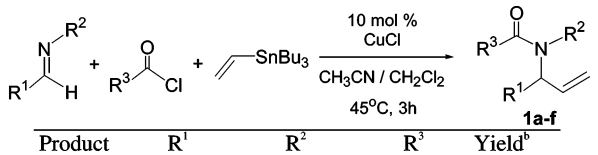
SCHEME 2. Postulated Mechanism of the Copper-Catalyzed Coupling

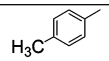
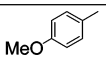
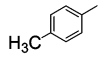
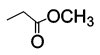
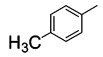


The use of copper(I) complexes as a replacement for palladium as the catalyst in intermolecular and intramolecular cross-coupling reactions involving organostannanes has been well-established through the research of Piers, Liebeskind, Falck, and others.[18] Mechanistically, these reactions have been postulated to proceed via the initial transmetalation of the organotin reagent to copper, followed by the formation of a transient Cu(III) species by oxidative addition. While a similar mechanism is possible here, it seems more plausible that the direct nucleophilic attack of the organocuprate intermediate on the electrophilic N-acyl iminium salt leads to product formation and regenerates the copper catalyst (Scheme 2).[19] Most of the previously developed copper-mediated cross-coupling reactions require superstoichiometric quantities of Cu(I) salts to drive the reactions to completion, likely due to the reversibility of the Sn−Cu transmetalation, where build-up of Bu_3SnCl causes a decrease in the reaction rate.[18a] In our case, we believe that the high electrophilicity of the substrate N-acyl iminium salt, which rapidly traps any in situ generated organocuprate, allows the reaction to proceed with only 10 mol % of CuCl catalyst.[22]

In addition to the practical utility of using copper(I) salts rather than palladium, this multicomponent coupling is also relatively general. As can be seen in Table 2, a range of R^1 and R^2 fragments can be incorporated via the imine substrate. For example, imines derived from aryl, heteroaryl, non-enolizable alkyl, and α,β-unsaturated (Table 3) aldehydes represent viable substrates. In contrast to our previously reported palladium catalyzed reaction, steric hindrance at the α-carbon of the imine does not seem to impede the reaction (**1c**, **1f**). Substitution at the imine nitrogen allows for the incorporation of alkyl, aryl, and allyl groups, as well as α-amino acid derived imine (**1b**). A variety of different functional

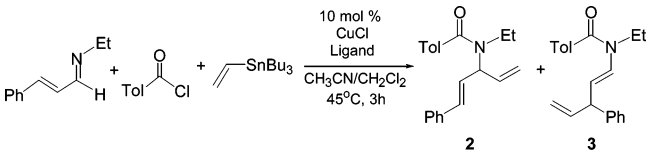
TABLE 2. Imine and Acid Chlorides in the Copper-Catalyzed Coupling[a]

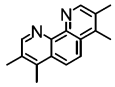


Product	R^1	R^2	R^3	Yield[b]
1a				76%
1b				82%
1c				85%
1d				81%
1e				88%
1f				72%

[a] 0.48 mmol of imine, 0.63 mmol of acid chloride, 0.48 mmol of organotin reagent, and 0.048 mmol of CuCl in CH_3CN (4 mL), and CH_2Cl_2 (3 mL) for 3 h. [b] Isolated yield.

TABLE 3. 1,2- versus 1,4-Addition with α,β-Unsaturated Imines[a]



Ligand[b]	Ratio of **2 : 3** (yield of major isomer)[c]
None	1 : 2.0 (50%)
LiCl	1 : 2.1 (53%)
Bu_4NBr	1 : 2.8 (62%)
Bu_4NI	1 : 3.8 (68%)
CuBr[d]	1 : 3.9 (56%)
CuI[d]	1 : 5.0 (55%)
	1.4 : 1 (51%)
	3 : 1 (64%)
	9.5 : 1 (76%)

[a] Reaction performed with 0.48 mmol of imine, 0.63 mmol of acid chloride, 0.48 mmol of organotin reagent, and 0.048 mmol of CuCl in CH_3CN (4 mL) and CH_2Cl_2 (3 mL) for 3 h. [b] Halide salt additives used in stoichiometric quantity (0.48 mmol). Nitrogen donor ligands in 12 mol % (0.053 mmol). [c] Isolated yield of major isomer of reaction. [d] Used as catalyst instead of CuCl.

(18) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609. (c) Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 9082. (d) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973.

(19) This mechanism is directly analogous to that which we and others have recently postulated for the addition of terminal alkynes to iminium salts[20] and in the copper-catalyzed conjugate addition of organostannanes and α,β-unsaturated ketones.[21]

(20) (a) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. (b) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (d) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347.

(21) (a) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641. (b) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322. (c) Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753, and references therein.

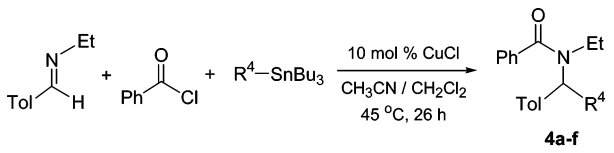
(22) A number of other copper(I) sources (e.g., CuBr, CuI, CuOTf, $CuPF_6$, and CuCN) are also effective catalysts for this reaction, albeit at slightly diminished yields (see the Supporting Information for details).

groups are well tolerated, including ethers, esters, tosylates, and halides. However, the use of enolizable imines leads to the formation of enamides upon addition of acid chloride, due to isomerization of the iminium salt substrate.[23] A wide array of small and bulky alkyl, aryl and heteroaryl substituted acid chlorides generate α-substituted amides in good yield. N-protected α-substituted amines can also be formed by replacing the acid chloride with a chloroformate, allowing the generation of both TROC and CBz (using 2,2,2-trichloroethyl chloroformate and benzyloxychloroformate, respectively) protected products (**1d**, **1e**).

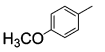
In the previously reported palladium catalyzed version of this reaction, ligands were found to generally inhibit catalysis, likely due to their slowing transmetalation to palladium.[13] In contrast, this copper-catalyzed reaction can tolerate the presence of various donor ligands, providing a useful handle to control features such as reaction selectivity. For example, under standard conditions, the catalytic coupling with a cinnamaldehyde-based imine (Table 3) leads to the formation of both 1,2- and 1,4-addition products in a 1:2 ratio. Upon addition of one equivalent of Bu_4NI, this selectivity can be enhanced to 1:3.8. This ratio can be further increased by employing CuI as the catalyst rather than CuCl (1:5 ratio). Alternatively, the addition of nitrogen donor ligands diverts selectivity to favor the formation of the 1,2-addition product, with up to 9.5:1 ratio using 3,4,7,8-tetramethyl-1,10-phenanthroline. Although the reasons for this selectivity difference are not fully understood, it seems likely that their influence is through modulating the reactivity of an in situ generated organocuprate complex. For example, the addition of halide salts to cuprates is known to favor the formation of the softer nucleophiles, such as $[RCuI]^-$, which undergo 1,4-addition more readily than their CuR counterparts.[24] It has also been shown that the addition of bulky ligands to cuprates favors 1,2-addition.[25] The highest level of 1,2-addition with the most sterically encumbered tetramethyl-1,10-phenanthroline ligand is consistent with this observation.

Perhaps most notable about this copper catalyzed coupling is the diversity of organotin reagents that can be employed (Table 4). While longer reaction times are required for reactions of nonvinylstannanes, the product yields remain good. Thus, the transfer of phenyl as well as substituted aromatic groups can all be achieved with this reaction. Interestingly, the coupling with 2-(tributylstannyl)thiophene, occurs far more readily (ambient temperature) than in the case of the aryl substituents. This is likely due to initial coordination of the thiophene fragment to the copper metal center, leading to a chelation-assisted transmetalation to copper.[18] Consistent with this postulate, the ortho-methoxyphenyl organostannane also reacted more rapidly than the other arylorganostannanes. Benzylation is also viable in this three-component coupling, and provides products in good yield.

TABLE 4. Organostannanes in the Copper-Catalyzed Coupling

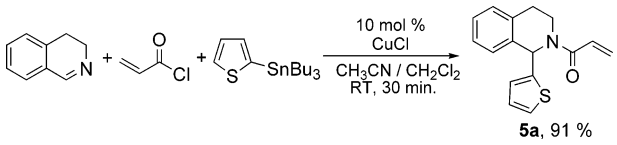


4a-f

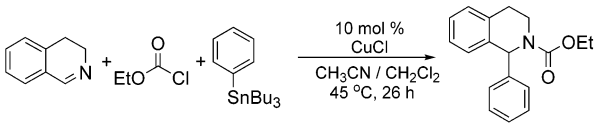
Product	R^4	Yield[b]
4a		84%
4b		91%[c]
4c		84%
4d		90%[d]
4e		93%
4f		69%[e]

[a] 0.48 mmol of imine and tin reagent, 0.63 mmol of acid chloride, and 0.048 mmol of CuCl in 4 mL of CH_3CN/3 mL of CH_2Cl_2. [b] Isolated yield. [c] 30 min at rt. [d] 15 h at 45 °C. [e] 48 h at 95 °C.

SCHEME 3. Synthesis of 5a and 5b



5a, 91 %



5b, 88 %

As a preliminary illustration of the utility of this reaction, we have probed its application to the construction of the antibacterially active **5a**,[26] as well as the PCP analogue **5b**.[27] Both of these products can be formed in a single step and in high yield from readily available and air stable reagents (Scheme 3). In light of the functional group compatibility of this reaction, a range of other structurally analogous isoquinoline alkaloids could also be easily formed using this process.

Conclusions

In summary, we have developed a copper-catalyzed multicomponent synthesis of α-substituted amides from imines, organotin reagents, and acid chlorides. Considering the simplicity of the catalyst, the generality of the reaction, and the stability of each of these reagents, this provides a straightforward method to construct a diverse array of α-substituted amides and N-protected amines. Studies directed toward the use of other transmetalating

(23) α-Chloroamides, or *N*-acyliminium chlorides, are established to undergo rapid HCl elimination to generate enamides. See: Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 1047.

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agents, as well as the control of stereoselectivity in the reaction, are currently underway.

Experimental Section

General Procedure for Catalytic Synthesis of α-Substituted Amides. The imine (0.48 mmol) and the acid chloride/chloroformate (0.62 mmol) were mixed in 3 mL of acetonitrile. This was added to a solution of CuCl (4.2 mg, 0.048 mmol) in 1 mL of dry acetonitrile. The reaction mixture was transferred to a 25 mL reaction bomb. The organostannane (0.48 mmol) in 3 mL of methylene chloride was added into the reaction mixture, which was then heated (if necessary) in a temperature regulated oil bath for 30 min to 48 h. The reaction mixture was then concentrated in vacuo and redissolved in 50 mL of ethyl acetate. Saturated KF solution (15 mL) was added and this mixture was stirred for 2 h. The white solid that formed was then filtered off through Celite, and the organic layer was separated, and washed with 2 × 50 mL of distilled H_2O. The KF solution was extracted with 2 × 50 mL of ethyl acetate, and the organic layers were combined and dried over anhydrous $MgSO_4$. The drying agent was then filtered off and the solvent removed in vacuo, and the residual crude product was purified with column chromatography using ethyl acetate/hexanes as eluent to afford the corresponding α-substituted amide.[28]

Furan-2-carboxylic acid (4-methoxyphenyl)(1-*p*-tolylallyl)amide (1a). Isolated yield: 76%. ^{1}H NMR (300 MHz, 60 °C, $CDCl_3$): δ 7.40 (s, 1H), 7.21−7.09 (m, 4H), 6.93−6.80 (m, 4H), 6.40 (d, 1H, J = 5.6 Hz), 6.27−6.14 (m, 2H), 5.73 (s, 1H), 5.42−5.31 (m, 2H), 3.79 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75.5 MHz, 60 °C, $CDCl_3$): δ 159.7, 158.9, 147.6, 144.7, 137.4, 136.7, 135.8, 132.8, 131.8, 129.0, 128.5, 118.4, 116.0, 114.2, 111.2, 63.0, 55.5, 20.5. IR (neat): ν = 1709 cm^{-1} (C=O). HRMS for $C_{22}H_{21}NO_3$: calcd 347.1521, found 347.1526.

[Isobutyryl(1-*p*-tolylallyl)amino]acetic Acid Methyl Ester (1b). Isolated yield: 82%. ^{1}H NMR (270 MHz, 20 °C, $CDCl_3$): δ 7.20−7.09 (m, 4H), 6.45 (d, 0.3H, J = 7.2 Hz, minor rotamer), 6.20−5.95 (m, 1H), 5.69 (d, 0.7H, J = 7.2 Hz, major isomer), 5.44−5.23 (m, 2H), 4.03−3.79 (m, 2H), 3.60 (s, 2.1H, major isomer), 3.50 (s, 0.9H, minor isomer), 2.99−2.86 (m, 0.7H, major rotamer), 2.67−2.54 (m, 0.3H, minor isomer), 2.32−2.32 (m, 3H), 1.21 (m, 6H). ^{13}C NMR (68.0 MHz, 20 °C, $CDCl_3$): for major and minor isomers, δ 178.0, 177.8, 170.0, 169.6, 137.8, 137.4, 135.7, 135.1, 134.8, 134.6, 129.3, 129.0, 128.6, 127.8, 118.6, 117.6, 62.4, 58.2, 52.0, 51.8, 45.9, 45.3, 31.2, 30.4, 21.0, 21.0, 19.8, 19.7, 19.5, 19.4. IR (neat): ν = 1648 cm^{-1} (C=O). HRMS for $C_{17}H_{23}NO_3$: calcd 289.1678, found 289.1675.

***N*-Benzyl-*N*-(1-*tert*-butylallyl)acetamide (1c).** Isolated yield: 85%. ^{1}H NMR (270 MHz, 130 °C, DMSO-d_6): δ 7.35−7.12 (m, 5H), 6.13−5.98 (m, 1H), 5.17−4.94 (m, 2H), 4.57 (s, 2H), 1.94 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (68.0 MHz, 130 °C, d^6-DMSO): δ 170.2, 138.5, 133.8, 127.3, 125.7, 125.6, 118.2, 48.9, 35.0, 26.9, 24.8, 21.5. IR (neat): ν = 1636 cm^{-1} (C=O). HRMS for $C_{16}H_{23}NO$: calcd 245.1780, found 245.1777.

Ethyl{1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]allyl}-carbamic Acid 2,2,2-Trichloroethyl Ester (1d). Isolated yield: 81%. ^{1}H NMR (270 MHz, 80 °C, CD_3CN): δ 7.97 (d, 1H, J = 7.9 Hz), 7.78 (d, 2H, J = 7.9 Hz), 7.55 (d, 2H, J = 6.2 Hz), 7.40−7.19 (m, 4H), 6.38−6.22 (m, 1H), 6.04 (d, 1H, J = 6.2 Hz), 5.40−5.31 (m, 2H), 4.86 (q, 2H, J = 6.5 Hz), 3.40−3.13 (m, 2H), 2.33 (s, 3H), 0.69 (t, 3H, J = 6.5 Hz). ^{13}C NMR (68.0 MHz, 80 °C, CD_3CN): δ 154.5, 146.1, 135.8, 135.3, 134.8, 130.3, 130.3, 137.0, 125.8, 125.5, 124.0, 122.1, 120.4, 117.8, 114.1, 96.3, 75.2, 55.4, 39.8, 20.8, 14.2. IR (neat): ν = 1649 cm^{-1} (C=O). HRMS for $C_{23}H_{23}N_2O_4S^{35}Cl_3$: calcd 528.0444, found 528.0449.

Benzyl(1-*p*-tolylallyl)carbamic Acid Benzyl Ester (1e). Isolated yield: 88%. ^{1}H NMR (270 MHz, 90 °C, DMSO-d_6): δ 7.40−7.04 (m, 14H), 6.22−6.07 (m, 1H), 5.82−5.71 (br, 1H), 5.23−5.05 (m, 4H), 4.59 (d, 1H, J = 9.2 Hz), 4.40 (d, 1H, J = 9.2 Hz), 2.27 (s, 3H). ^{13}C NMR (68.0 MHz, 90 °C, DMSO-d_6): δ 155.2, 138.3, 136.2, 136.0, 135.9, 135.5, 128.3, 127.6, 127.4, 127.1, 126.9, 126.8, 126.6, 126.0, 117.3, 66.0, 62.2, 48.3, 19.9. IR (neat): ν =1693 cm^{-1} (C=O). HRMS for $C_{25}H_{25}NO_2$: calcd 371.1885, found 371.1879.

***N*-Allyl-*N*-[1-(2,6-dichlorophenyl)allyl]-4-iodobenzamide (1f).** Isolated yield: 72%. ^{1}H NMR (270 MHz, 80 °C, CD_3CN): δ 7.63 (d, 2H, J = 6.4 Hz), 7.30 (t, 4H, J = 6.4 Hz), 7.20−7.05 (m, 4H), 6.50−6.34 (m, 1H), 6.20 (d, 1H, J = 9.2 Hz), 5.26−4.98 (m, 4H). ^{13}C NMR (68.0 MHz, 80 °C, CD_3CN): δ 171.0, 137.7, 137.0, 135.8, 134.6, 133.6, 132.2, 129.8, 129.6, 129.2, 128.9, 119.7, 95.1, 63.0, 48.4. HRMS for $C_{19}H_{16}NO^{35}Cl_2I$: calcd 470.9654, found 470.9647. IR (neat): ν = 1642 cm^{-1} (C=O).

***N*-Ethyl-4-methyl-*N*-(3-phenyl-1-vinylallyl)benzamide (2).** Isolated yield: 77%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN): δ 7.43−7.08 (m, 9H), 6.42 (d, 1H, J = 6.9 Hz), 6.29 (dd, 1H, J = 0.7, 6.9 Hz), 6.11−5.96 (m, 1H), 5.22−5.00 (m, 3H), 3.58−3.21 (m, 2H), 2.27 (s, 3H), 1.07 (t, 3H, J = 6.9 Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 171.7, 139.6, 137.3, 137.0, 135.4, 132.7, 129.2, 128.9, 128.1, 126.7, 126.6, 115.5, 115.3, 61.8, 39.8, 20.6, 14.8. IR (neat): ν = 1635 cm^{-1} (C=O). HRMS for $C_{21}H_{23}NO$: calcd 305.1780, found 305.1775.

***N*-Ethyl-4-methyl-*N*-(3-phenylpenta-1,4-dienyl)benzamide (3).** Isolated yield 53%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN): δ 7.42−7.23 (m, 9H), 6.54−6.49 (m, 1H), 6.18−6.02 (m, 1H), 5.97−5.84 (m, 1H), 5.04−4.89 (m, 2H), 3.91 (t, 1H, J = 6.9 Hz), 3.70 (q, 2H, J = 6.7 Hz), 2.47 (s, 3H), 1.26 (t, 3H, J = 4.9 Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 170.0, 143.8, 141.3, 141.3, 140.5, 133.8, 129.7, 129.1, 128.8, 128.1, 127.8, 126.6, 114.5, 114.0, 103.6, 50.3, 39.2, 20.6, 12.0. IR (neat): ν = 1641 cm^{-1} (C=O). HRMS for $C_{21}H_{23}NO$: calcd 305.1780, found 305.1776.

***N*-Ethyl-*N*-(phenyl-*p*-tolylmethyl)benzamide (4a).** Isolated yield: 84%. ^{1}H NMR (270 MHz, 80 °C, DMSO-d_6): δ 7.49−7.04 (m, 14H), 6.34 (s, 1H), 3.38 (q, 2H, J = 6.7 Hz), 2.31 (s, 3H), 0.63 (t, 3H, J = 7.2 Hz). ^{13}C NMR (68.0 MHz, 80 °C, DMSO-d_6): δ 170.5, 140.1, 137.9, 136.9, 136.9, 129.2, 129.1, 128.6, 128.5, 128.5, 128.5, 127.5, 126.2, 64.3, 40.2, 20.6, 14.1. IR (neat): ν = 1628 cm^{-1} (C=O). HRMS for $C_{23}H_{23}NO$: calcd 329.1780, found 329.1777.

***N*-Ethyl-*N*-(thiophene-2-yl-*p*-tolylmethyl)benzamide (4b).** Isolated yield: 91%. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$): δ 7.47−7.10 (m, 10H), 6.98 (t, 1H, J = 5.2 Hz), 6.89 (d, 1H, J = 5.2 Hz), 6.57 (s,1H), 3.51 (q, 2H, J = 6.9 Hz), 2.35 (s, 3H), 0.79 (t, 3H, J = 6.9 Hz). ^{13}C NMR (68.0 MHz, 80 °C, DMSO-d_6): δ 171.8, 143.8, 137.8, 137.3, 136.3, 129.3, 129.2, 128.5, 128.3, 127.0, 126.8, 126.4, 125.3, 59.4, 40.2, 21.0, 14.0. IR (neat): ν = 1622 cm^{-1} (C=O). HRMS for $C_{21}H_{21}NOS$: calcd 335.1344, found 335.1347.

***N*-Ethyl-*N*-[(4-methoxyphenyl)-*p*-tolylmethyl]benzamide (4c).** Isolated yield: 84%. ^{1}H NMR (270 MHz, 75 °C, DMSO-d_6): δ 7.98−7.86 (m, 5H), 7.75−7.60 (m, 6H), 7.45 (d, 2H, J = 9.8 Hz), 6.86 (s, 1H), 4.34 (s, 3H), 4.08−3.88 (m, 2H), 2.88 (s, 3H), 1.20 (t, 3H, J = 6.9 Hz). ^{13}C NMR (68.0 MHz, 75 °C, DMSO-d_6): δ 170.9, 158.7, 137.5, 136.7, 136.6, 131.5, 129.4, 128.4, 128.3, 127.9, 127.7, 125.5, 113.4, 63.4, 54.5, 39.4, 19.4, 12.8. IR (neat): ν = 1657 cm^{-1} (C=O). HRMS for $C_{24}H_{25}NO_2$: calcd 359.1885, found 359.1891.

***N*-Ethyl-*N*-[(2-methoxyphenyl)-*p*-tolylmethyl]benzamide (4d).** Isolated yield: 90%. ^{1}H NMR (270 MHz, 60 °C, $CDCl_3$): δ 7.37−7.24 (m, 6H), 7.16 (d, 2H, J = 5.2 Hz), 7.04 (d, 2H, J = 5.2 Hz), 6.98−6.81 (m, 3H), 6.52−6.33 (s, 1H), 3.88−3.65 (m, 4H), 3.32−3.19(m, 1H), 2.39 (s, 3H), 0.73 (t, 3H, J = 6.9 Hz). ^{13}C NMR (68.0 MHz, 100 °C, DMSO-d_6): δ 170.6, 157.0, 137.3, 136.6, 135.6, 128.9, 128.5, 128.4, 128.2, 127.9, 127.3, 126.9, 125.4, 119.7, 110.8, 58.7, 54.9, 39.3, 19.9, 12.8.

(28) All ^{1}H and ^{13}C NMR spectra of the products were obtained at elevated temperatures in order to equilibrate interconverting amide rotomers.

IR (neat): $\nu = 1625$ cm^{-1} (C=O). HRMS for $C_{24}H_{25}NO_2$: calcd 359.1885, found 359.1880.

***N*-Ethyl-*N*-[(4-fluorophenyl)-*p*-tolylmethyl]benzamide (4e).** Isolated yield: 93%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN): δ 7.37−7.25 (m, 5H), 7.21−7.10 (m, 4H), 7.07−6.96 (m, 4H), 6.31 (s, 1H), 3.38 (q, 2H, $J = 6.9$ Hz), 2.27 (s, 3H), 0.61 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 171.9, 138.2, 137.8, 137.1, 136.7, 130.9, 130.8, 129.4, 128.9, 128.7, 126.4, 115.5, 115.2, 64.1, 40.6, 20.3, 13.8. IR (neat): $\nu = 1631$ cm^{-1} (C=O). HRMS for $C_{23}H_{22}NOF$: calcd 347.1685, found 347.1682.

***N*-Ethyl-*N*-(2-phenyl-1-*p*-tolylethyl)benzamide (4f).** Isolated yield: 69%. ^{1}H NMR (270 MHz, 110 °C, DMSO-d_6): δ 7.42−6.94 (m, 14H), 5.35 (t, 1H, $J = 6.9$ Hz), 3.34 (d, 2H, $J = 5.2$ Hz), 3.19 (m, 2H), 2.23 (s, 3H), 0.68 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (68.0 MHz, 110 °C, DMSO-d_6): δ 170.2, 137.9, 137.3, 136.2, 136.0, 128.5, 128.3, 128.0, 127.5, 127.4, 127.1, 125.5, 125.4, 59.7, 38.2, 36.5, 19.8, 13.6. IR (neat): $\nu = 1634$ cm^{-1} (C=O). HRMS for $C_{24}H_{25}NO$: calcd 343.1936, found 343.1932.

1-(1-Thiophene-2-yl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propenone (5a). Isolated yield: 91%. ^{1}H NMR (270 MHz, 90 °C, DMSO-d_6): δ 7.36 (d, 1H, $J = 4.9$ Hz), 7.30−7.15 (m, 4H), 6.96−6.66 (m, 4H), 6.18 (dd, 1H, $J = 2.2$, 16.8 Hz), 5.72 (d, 1H, $J = 2.2$, 16.8 Hz), 4.10 (br, 1H), 3.42 (br, 1H), 3.01−2.76 (m, 2H). ^{13}C NMR (68.0 MHz, 90 °C, DMSO-d_6): δ 164.3, 145.8, 134.7, 133.8, 128.2, 128.2, 127.5, 126.8, 126.8, 126.8, 125.9, 125.5, 125.0, 51.9, 38.3, 27.6. IR (neat): $\nu = 1644$ cm^{-1} (C=O). HRMS for $C_{16}H_{15}NOS$: calcd 269.0874, found 269.0868.

***N*-Ethyl-*N*-(2-phenyl-1-*p*-tolylethyl)benzamide (5b).** Isolated yield: 88%. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$): δ 7.34−7.03 (m, 9H), 6.42 (s, 1H), 4.32−4.04 (m, 3H), 3.37−3.23 (m, 1H), 3.06−2.92 (m, 1H), 2.83−2.70 (m, 1H), 1.31 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (68.0 MHz, 55 °C, $CDCl_3$): δ 155.5, 142.7, 135.5, 135.0, 128.7, 128.4, 128.2, 128.1, 127.2, 126.9, 126.0, 61.3, 57.7, 38.1, 28.3, 14.6. IR (neat): $\nu = 1687$ cm^{-1} (C=O). HRMS for $C_{18}H_{19}NO_2$: calcd 281.1416, found 281.1407.

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Supporting Information Available: Spectral data for products **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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