Direct Access to Chiral Secondary Amides by Copper-Catalyzed Borylative Carboxamidation of Vinylarenes with Isocyanates

Daniele Fiorito,[†] Yangbin Liu,[†] Céline Besnard,[‡] Clément Mazet*,[†]

[†] Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva, Switzerland.

[‡] Laboratory of Crystallography, University of Geneva, 24 quai Ernest Ansermet, 1211 Geneva, Switzerland.

ABSTRACT: A Cu-catalyzed borylative carboxamidation reaction has been developed using vinylarenes and isocyanates. Alkynes, branched 1,3-dienes and bicyclic alkenes were also found to be competent coupling partners. Using a chiral phosphanamine ligand, an enantioselective variant of this transformation was developed, affording a set of α-chiral amides with unprecedented levels of enantioselectivity. The synthetic utility of the method was demonstrated through a series of representative stereoretentive post-catalytic derivatizations.

■ INTRODUCTION

The amide bond is undoubtedly one of the most prevalent structural motifs found in natural and synthetic molecules with numerous applications in the pharmaceutical, agrochemical and polymer industries (Figure 1, A).[1] The dehydrative condensation of an amine and a carboxylic acid mediated by elaborated coupling reagents remains the most widely used strategy for amide bond formation, despite the excessive waste and expenses associated with this approach.[2] With the growing environmental and economic concerns of the 21st century, recent years have witnessed a renewed interest in developing alternative methods that – ideally – would be catalytic, atom-economic, broadly applicable and that would rely on the use of inexpensive reagents. Several innovative protocols that do fulfill some of these objectives have been devised over the last decade.[3] In this context, isocyanates have been recognized as an attractive electrophilic building block for alternative amide synthesis by C–C bond formation strategies rather than the conventional C–N bond formation approach.[4] This led in particular to the development of (i) effective non-catalytic amidations using hindered and unhindered Grignard reagents,[5] (ii) several transition metal-catalyzed amidations using organoboron or organotin reagents for the preparation of aromatic amides,[6] (iii) Ni-catalyzed reductive amidations of C–O electrophiles, aryl and alkyl halides,[7] (iv) Ni/photoredox catalyzed amidations using alkylsilicate reagents.[8] Despite these remarkable advances, there is still a pressing need to expand the current portfolio of catalytic processes to protocols that rely on abundant low-cost starting materials. Specifically, the development of a catalytic method for the addition of isocyanates to readily available alkenes would provide an environmentally sustainable and cost-effective access to biologically relevant chiral secondary amides while offering the possibility to engineer an enantioselective variant of this coupling reaction. This would constitute a remarkable step forward in amide synthesis as - to the best of our knowledge - there is currently no example of an intermolecular enantioselective coupling reaction between isocyanates and simple alkenes that produces α-chiral amides with high levels of stereocontrol.

The direct addition of isocyanates to olefins remains largely unexplored (Figure 1, B).[9-10] In the mid-1980s, Hoberg developed a Ni-mediated, and subsequently a Ni-catalyzed, coupling between phenyl isocyanate and ethylene to afford *N*-phenylacrylamide.[10a,b] Later, Jamison was able to favor formation of 1,1-disubstituted acrylamides using α-olefins and a bulky *N*-heterocyclic carbene as supporting ligand to nickel.[10d] These reactions are proposed to proceed via a transient azanickelacyclopentanone which undergoes β-H elimination. Murakami showed that if acrylates were employed under otherwise relatively similar conditions, 1,3,5-trisubstituted hydantoins were isolated in very good yield.[10e] Matsuda described a three-component racemic Rh-catalyzed amidation of α,β-unsaturated ketones using aryl or alkyl isocyanates and a silane as hydride source.[10c] The reaction was proposed to pass by the formation of a high-valent [(R_3Si)Rh-*O*-enolate] complex. The 1,3-amido esters thus generated were usually obtained in good yield.

As part of our research program on the development of selective functionalizations of olefins,[11] we recently reported a Cu-catalyzed enantioselective 1,2-borylation of 2-substituted 1,3-dienes.[11c] This study was inspired by the numerous examples of Cu-catalyzed borylative couplings of olefins that have been described in the past few years.[12] Mechanistically, these reactions consist in intercepting a nucleophilic Cu intermediate with various electrophiles ranging from a simple proton to C-, N- or O-centered electrophiles.[13-16] Dual catalytic processes in which such Csp^3 Cu-nucleophiles are transmetallated to a Pd(aryl) intermediate or an organostanane derivative led to the development of elegant difunctionalizations of alkenes.[17] Importantly, most of these transformations require activated olefins to reach acceptable efficiency. Use of simple and

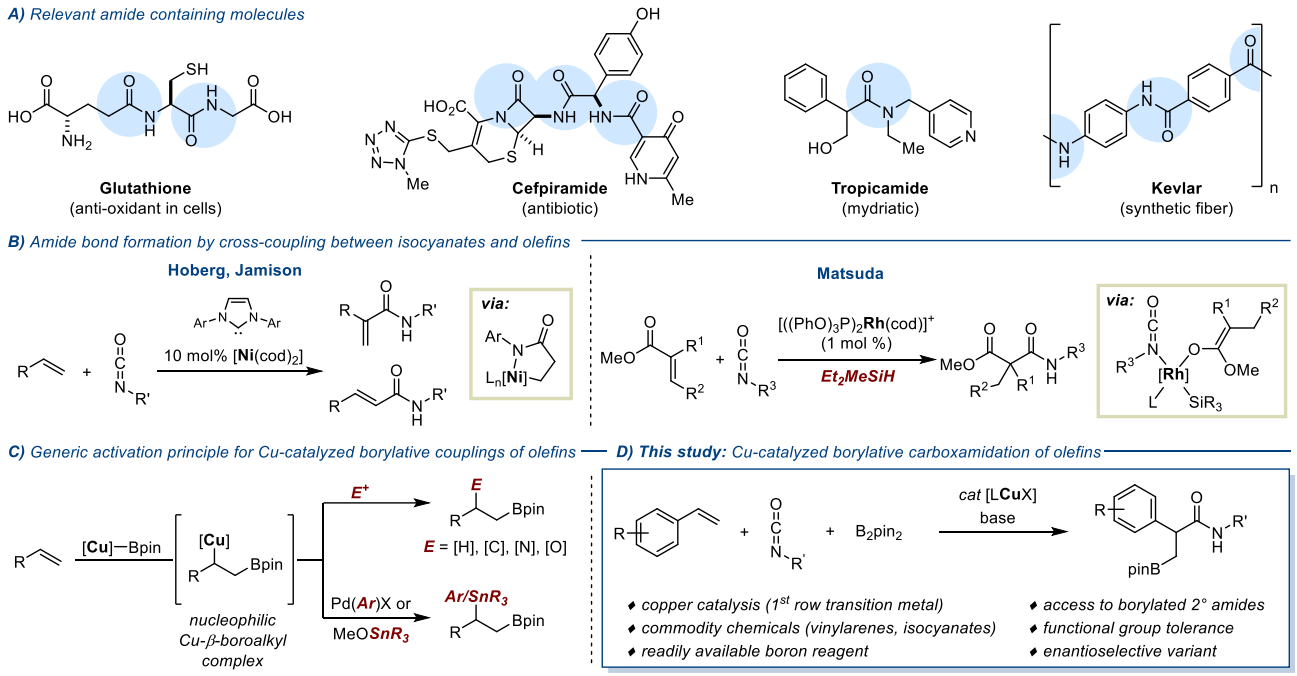


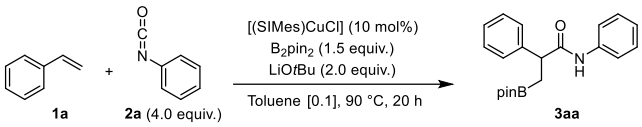
Figure 1. (A) Representative amide-containing molecules. (B) Precedents in metal-catalyzed coupling between isocyanates and alkenes. (C) Generic activation principle in Cu-catalyzed borylative couplings of alkenes. (D) Cu-catalyzed borylative carboxamidation of alkenes.

unactivated alkenes is much less common (Figure 1, C).[15c,16] We hypothesized that a similar strategy could be followed to devise a Cu-catalyzed borylative carboxamidation of olefins – provided the nucleophilic organocopper intermediate would undergo productive coupling with sensitive electrophilic isocyanates under the necessarily basic conditions (Figure 1, D). Herein, we report that the requisite reactivity could be achieved, enabling access to chiral secondary amides bearing a α-stereocenter and a β-boronate handle with good to excellent yields. Alkynes were also found to be competent coupling partners leading to β-borylated acrylamides. With slight modification of the reaction conditions, an enantioselective variant of this transformation was developed, affording a set of α-chiral amides with unprecedented levels of enantioselectivity with highly electrophilic isocyanates. Finally, the synthetic utility of this transformation was demonstrated through a series of representative (stereoretentive) derivatizations.

■ RESULTS AND DISCUSSION

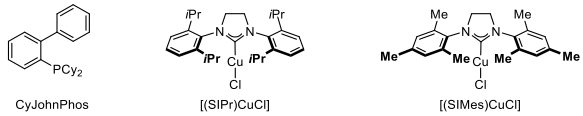
We began our study by investigating the reaction between styrene **1a**, phenylisocyanate **2a** and bis(pinacolato)diboron under conditions favorable for the formation of transient Cu β-boroalkyl complexes (Table 1). Upon evaluating a range of parameters, we rapidly identified that the coupling reaction can be achieved using [(SIMes)CuCl] as catalyst, LiO*t*Bu as base in toluene at 90 °C, delivering **3aa** in 82% yield (Table 1, Entry 1). No reaction was observed if the precatalyst was substituted by CuCl and much reduced conversions were obtained with other *N*-heterocyclic ligands or monophosphines (Entry 3-7). Of note, CyJohnPhos proved nearly as effective as [(SIMes)CuCl] (Entry 8). Use of other inorganic bases (Entry 9-11) and solvent variations

Table 1. Reaction optimization[a]



1a 2a (4.0 equiv.) 3aa

entry	Variation from optimized conditions	Conv. (%)[b]
1	none	90 (82)[c]
2	CuCl instead of [(SIMes)CuCl]	0
3	[(SIPr)CuCl] instead of [(SIMes)CuCl]	19
4	10 mol% CuCl, 12 mol% PPh_3	24
5	10 mol% CuCl, 12 mol% $PPhCy_2$	21
6	10 mol% CuCl, 12 mol% PCy_3	54
7	10 mol% CuCl, 12 mol% P*t*Bu_3	65
8	10 mol% CuCl, 12 mol% CyJohnPhos	80
9	KO*t*Bu instead of LiO*t*Bu	51
10	NaO*t*Bu instead of LiO*t*Bu	27
11	CsF instead of LiO*t*Bu	16
12	THF instead of toluene	30
13	DMF instead of toluene	<5
14	5 mol%[(SIMes)CuCl], 3.0 equiv. **2a**, 1.2 equiv. B_2pin_2, 1.5 equiv. LiO*t*Bu	91 (75)[c]



[a] 0.15 mmol scale. [b] Determined by ^{1}H NMR of the crude reaction mixture using an internal standard. [c] Isolated yield after purification by column chromatography.

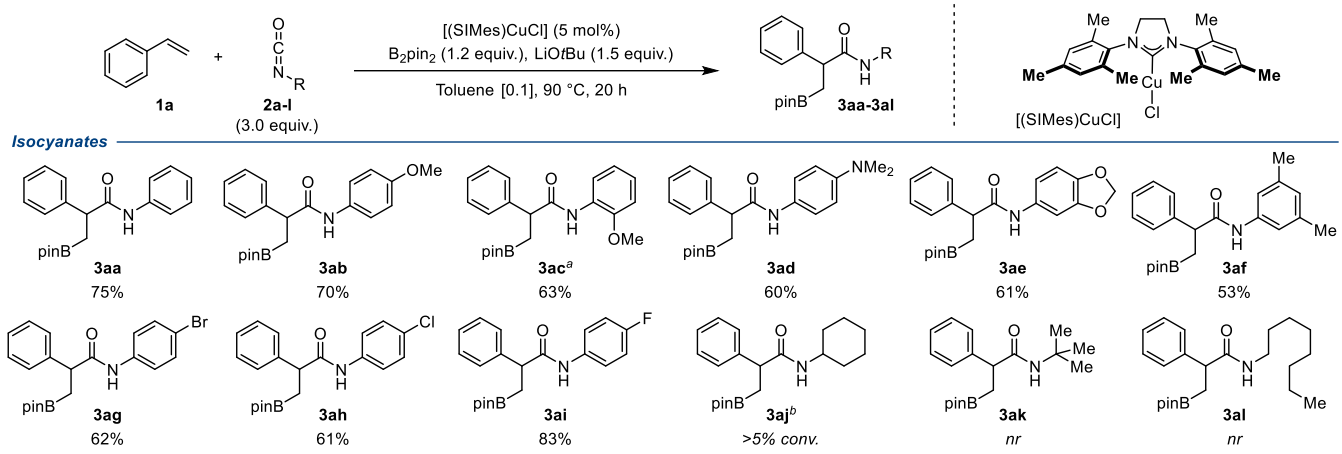


Figure 2. Effect of the structure of the isocyanate on the Cu-catalyzed borylative carboxamidation of styrene (0.3 mmol scale). [a] [(SIMes)CuCl] 10 mol%. [b] Determined by ^{1}H NMR using an internal standard.

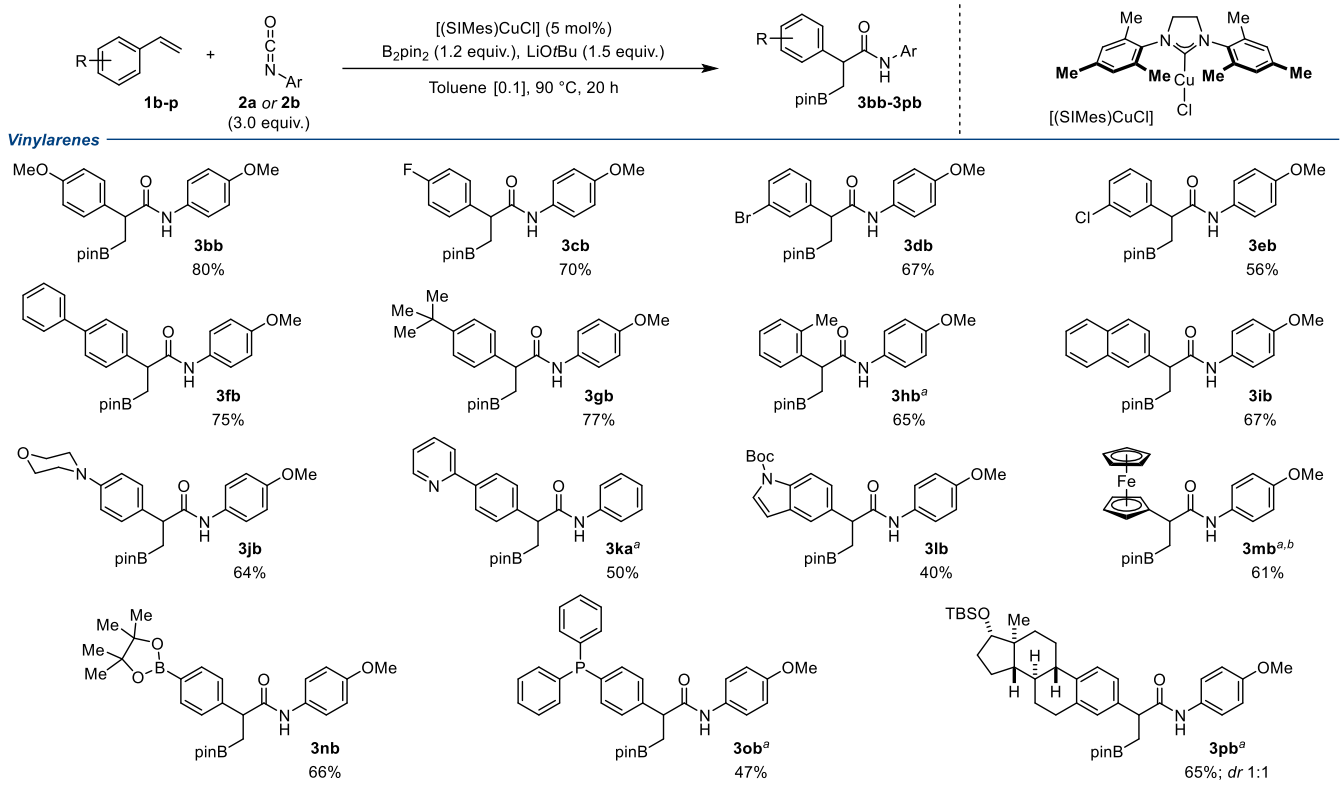


Figure 3. Cu-catalyzed borylative carboxamidation of vinylarenes (0.3 mmol scale). Yields of isolated product after purification. [a] [(SIMes)CuCl] 10 mol%. [b] 48 h.

(Entry 12-13) both had a detrimental impact on reactivity. A final round of optimization enabled to substantially decrease the catalyst loading (5 mol%) as well as the stoichiometry in **2a** (3.0 equiv.), in bis(pinacolato)diboron (1.2 equiv.) and in base (1.5 equiv.), while maintaining an excellent reactivity (75% yield, Entry 14).

Under these conditions, the scope of the reaction was examined with emphasis being placed first on isocyanates (Figure 2). The coupling reaction occurred in good to excellent yield with aryl isocyanates substituted by electron-donating or electron-withdrawing groups (53-80%). Substitution at the *ortho* position was tolerated but required increased loading in catalyst to achieve similar efficiency (**3ac**: 63% yield with 10 mol% [(SIMes)CuCl]). Alkyl isocyanates proved more challenging to couple. While with cyclohexyl isocyanate the product of borylative carboxamidation was formed in low conversion, no reactivity was observed with *n*-octyl- and *tert*-butyl-isocyanates **2k-l**. We tentatively attribute this reactivity difference to the lower electrophilicity of alkyl isocyanates and to the increased stability of the in situ generated carbamates, allophanates, and isocyanate dimers.[18]

The scope of vinylarenes was investigated using in most cases isocyanate **2b**, as methods for the deprotection of related secondary arylamides have been reported (Figure 3).[19] Styrenes substituted in *para* position with electron-dona

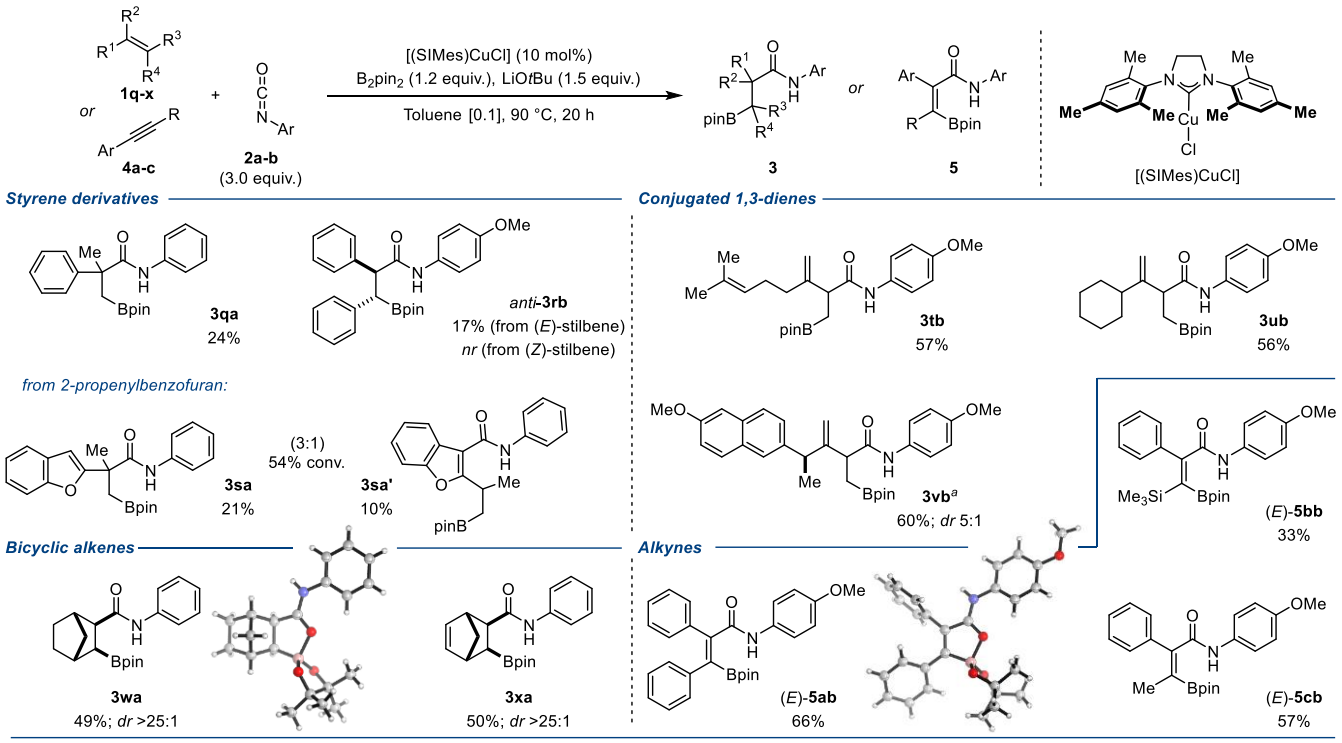


Figure 4. Cu-catalyzed borylative carboxamidation of styrene derivatives, 1,3-dienes, bicyclic alkenes and alkynes (0.2-0.3 mmol scale). Yields of isolated product after purification. [a] [(SIMes)CuCl] 15 mol%.

ting (**3bb**, **3gb**, **3jb**) or electron-withdrawing (**3cb**, **3fb**) substituents reacted efficiently. Substrates with a *meta* bromo- (**3db**) or *meta* chloro-substitutent (**3eb**) as well as an *ortho* methyl substituent (**3hb**) required 10 mol% of catalyst to reach practical yields. A pyridine-containing substrate (**3ka**), a protected 5-vinyl indole (**3lb**), 2-vinylnaphthalene (**3ib**) and vinylferrocene (**3mb**) were also competent olefinic coupling partners (40-80% yield). Functionalizable styrenes bearing a *para* a bis(pinacolato)boron (**3nb**) or a unusual diphenylphosphine (**3ob**) unit underwent effective borylative carboxamidation. Similarly, our protocol was successfully applied to a derivative with a stereochemically complex estradiol-derived scaffold affording **3pb** in 65% yield and 1:1 *dr*.

To evaluate the limits of our approach, α- and β-substituted styrenes were evaluated next (Figure 4).[20] Starting from α-methylstyrene, an amide which possesses a congested α-quaternary center could be prepared, albeit in very modest yield (**3qa**). While (*E*)-stilbene afforded *anti*-**3rb** in very low yield, no reaction was observed with (*Z*)-stilbene, even with increased catalyst loading, higher temperature and prolonged reaction time. When 2-propenylbenzofuran was employed, the expected coupling product **3sa** was isolated in only 21% yield. This was accompanied by formation of the constitutional isomer **3sa'** (10% yield), isomer which likely results from a 1,3-Cu shift and temporary dearomatization of the benzofuran core prior to product formation. We note that there are only scattered examples of related processes in the literature.[14b,m] As part of our work on conjugated dienes functionalization,[11c-e] several 2-substituted 1,3-dienes were successfully engaged in the borylative carboxamidation. This was quite unexpected as cycloaddition reactions between isocyanates and dienes have been reported under thermal conditions and/or using group X transition metals.[21] Thus, myrcene (**3tb**), 2-cyclohexyl-1,3-diene (**3ub**) and an enantiopure substrate derived from naproxen (**3vb**) all afforded the corresponding amides, with exquisite regioselectivity and in yields ranging from 57-60%. Activated bicyclic alkenes underwent coupling using our protocol. The bifunctional products were isolated as single diastereoisomers in moderate yield (**3wa**: 49%; **3xa**: 50%). Starting from internal alkynes, β-borylated acrylamides (*E*)-**5ab**, (*E*)-**5bb** and (*E*)-**5bc** were obtained as single stereoisomers and regioisomers, albeit in low to moderate yields (33-66%).[22] X-ray analyses of **3wa** and (*E*)-**5ab** showed an interaction between the oxygen atom of the amide function and the (pinacolato)boron unit leading to partial pyramidalization of the boron atom (B···O=C ~1.6 Å, torsion angle ~25°). Of note, the ^{11}B NMR solution measurements of all the borylated secondary amides reported in this study displayed chemical shifts ranging from 32 to 34 ppm - values that are typical of sp^2 hybridized boron atoms.

We subsequently set out to develop an enantioselective variant of the Cu-catalyzed borylative carboxamidation of alkenes (Figure 5). Styrene **1a** and phenyl isocyanate **2a** were selected as model coupling partners using the first set of optimized conditions disclosed in Table 1 (Entry 1). Copper complexes supported by chiral *N*-heterocyclic ligands were examined. Much to our dismay, no product formation was observed with (*R,R*)-**6a** – a complex that has proven effective in a number of Cu-catalyzed enantioselective carbofunctionalization of alkenes.[17g] Very low conversions were measured with (*R,R*)-**6b** and (*R,R*)-**6c**, the latter providing **3aa** in 81.5:18.5 *er*.[23] An extensive survey of chiral (P,P), (P,N) or monophosphine ligands was also conducted and representative results obtained with **6d-i** are collected

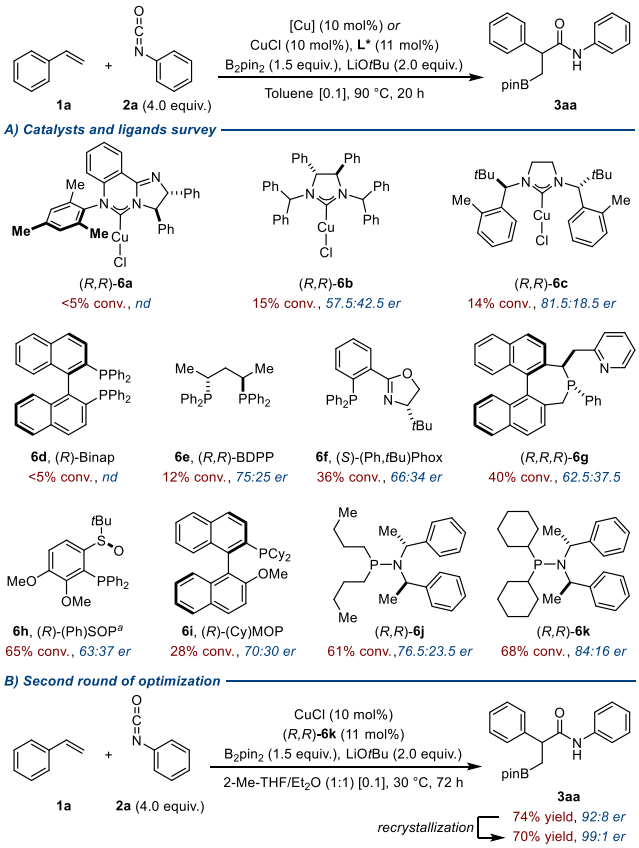


Figure 5. Enantioselective Cu-catalyzed borylative carboxamidation of styrene (0.15 mmol scale). (A) Catalysts and ligands survey. Conversion determined by ^{1}H NMR using an internal standard. *Er* determined by HPLC. (B) Optimized reaction conditions. [a] Reaction run at 50 °C.

in Figure 5-A (For a full scope, see Supporting Information). In all cases, reactivity remained problematic and the enantiomeric ratio never exceeded 75:25 *er*. Among the monophosphine ligands surveyed, a balanced result was obtained in terms or reactivity and selectivity with phosphanamine **6j** (61 % conv., 76.5:23.5 *er*).[11c,24] The modularity of the scaffold prompted us to investigate other members of this ligand class and, **3aa** was obtained in 68% conversion and a promising 84:16 *er* with **6k**. Additional optimizations were conducted with systematic variation of the solvent, base, temperature, relative stoichiometry and reaction time. This led to the identification of a final set of optimal conditions with which **3aa** was isolated in 74% yield and 92:8 *er* (Figure 5, B). Noticeably, the optical purity of the α-chiral secondary amide could be enhanced to 99:1 *er* upon a single recrystallization.

The scope of the enantioselective borylative carboxamidation of vinylarenes was examined with this protocol using ligand (*R,R*)-**6k**. We soon observed that variation of the electronic properties of the isocyanate severely impacted the enantiomeric ratio of the product. While the use of electron-deficient aryl isocyanates afforded the products in good yield and high enantioselectivity, the introduction of electron-donating substituents had a detrimental impact on the reactivity and selectivity of the catalytic system. These preliminary observations prompted us to investigate the electronic influence of both coupling partners in a

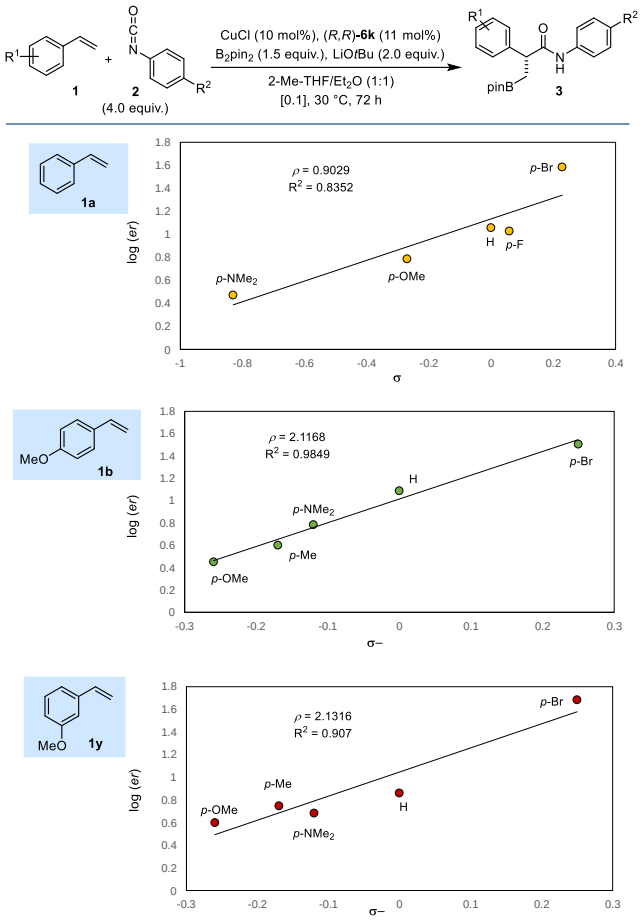


Figure 6. Hammett plots for the carboxamidation of substituted aryl isocyanates with styrene derivatives **1a**, **1b** and **1y** (0.15 mmol scale).

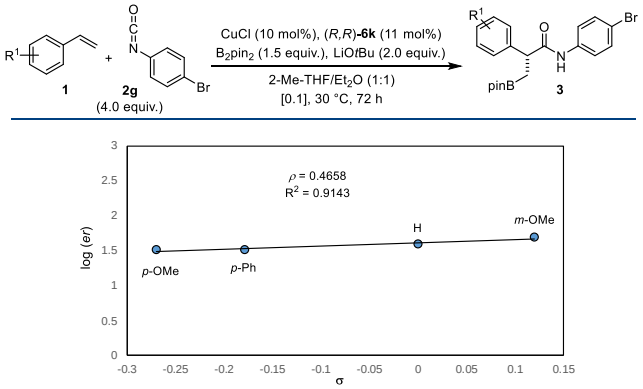


Figure 7. Hammett plots for the carboxamidation of substituted styrene derivatives using 4-bromophenyl isocyanate **2g** (0.15 mmol scale).

linear-free energy relationship study (LFER) where the enantiomeric ratio of the borylative carboxamidation products was plotted as a function of the Hammett parameters of *para* substituted aryl isocyanates for **1a, 1b** and **1y** (Figure 6).[25] Overall, the observed enantiomeric ratio measured correlated linearly with the σ values for **1a** and the σ– value for **1b** and **1y**. The highest levels of enantio-discrimination were observed with the most electron-deficient 4-bromophenyl isocyanate, leading to *er* ranging from 97:3 to 98:2. When the Hammett plot of the logarithm of the enantiomeric ratio against σ was constructed in the reaction

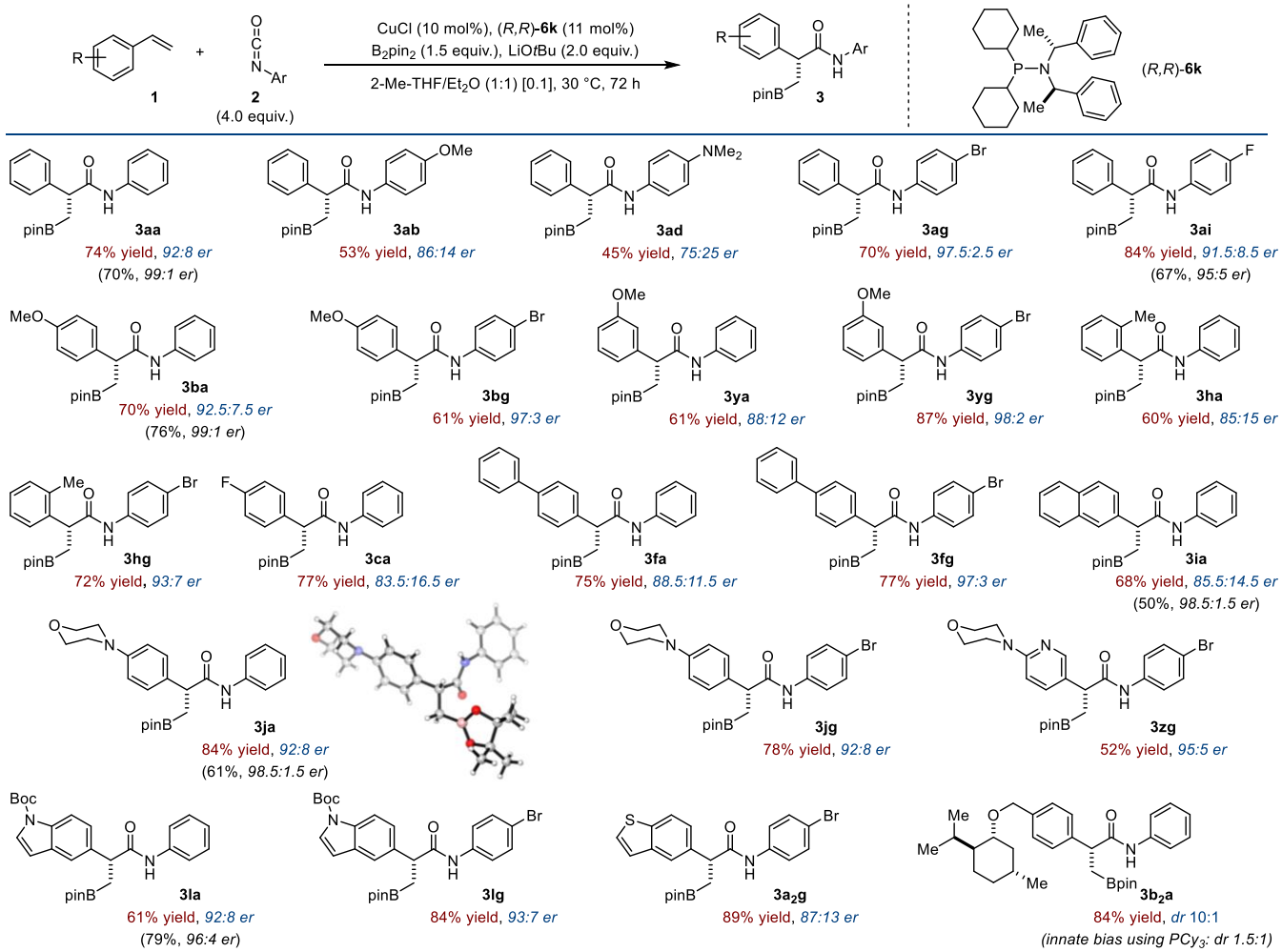


Figure 8. Enantioselective Cu-catalyzed borylative carboxamidation of vinylarenes (0.15-0.3 mmol scale). Yield of isolated product after purification. *Er* determined by HPLC. In parenthesis, yield and *er* refer to the result of a single recrystallization.

between various styrene derivatives and *p*-Br-aryl isocyanate, a nearly zero-slope linear correlation was obtained (Figure 7). Importantly, control experiments in which the enantiomeric ratio was measured over time as the catalytic reaction progressed indicated the absence of any enantiomerization process under the basic conditions employed. Even though it is premature to draw firm conclusions on the underlying mechanism governing reactivity and selectivity in the present Cu-catalyzed carboxamidation of alkenes, collectively, our results suggest that aryl isocyanates are involved in the stereochemistry-determining step of the carboxamidation process, whereas styrene derivatives are likely not. Indeed, the Cu-β-borobenzyl intermediate (C, Figure 1) could either be formed non-stereoselectively or could be susceptible to enantiomerization. For instance, partial enantiomerization could occur by a β-hydride elimination in a process resembling those proposed by Sadighi, Marder and Hoveyda.[14g,26] Alternatively, formation of a Cu-π-benzyl intermediate by a rapid σ-π-σ equilibrium followed by intermolecular π-benzyl exchange could also account for reduced selectivity. This latter hypothesis finds support in the Cu-catalyzed regioselective *ortho*-cyanation of vinylarenes disclosed by Yang and Buchwald as well as in the observation of **3sa**' in the Cu-catalyzed carboxamidation of 2-propenylbenzofuran (*vide supra*).[14b,14m,27] Subsequently, nucleophilic addition of the Cu-benzyl complex to aryl isocyanates could become the stereo-determining step, with the most electrophilic substrates affording the highest enantiomeric ratio.

With these notions in mind, we set out to delineate further the scope of the enantioselective version of the Cu-catalyzed borylative carboxamidation of vinylarenes. An overview of the results obtained is disclosed in Figure 8.[28] Noticeably, the products of carboxamidation were usually obtained in moderate to very good yield (45-89%; average yield = 68%; 23 examples). As it could be anticipated from the Hammett correlations, electron-rich aryl isocyanates gave moderate *er*, while electron-deficient aryl isocyanates led to much higher stereoselectivity levels. Excellent enantiomeric ratio were usually obtained with 4-bromophenyl isocyanate **2g** (typically >95:5 *er*). To demonstrate that the catalytic system is not limited to a single aryl isocyanate, we showed that the enantiomeric ratio of compounds that were obtained using less electrophilic derivatives could be enriched to >95:5 *er* upon a single recrystallization (**3aa**, **3ai**, **3ba**, **3ia**, **3ja**, **3la**). Aside from electronic considera-

tions, the sterically demanding *ortho*-methyl styrene affected reaction efficiency only marginally, delivering the coupling product in 60-72% yield (**3ha, 3hg**). Heterocycles such as pyridine (**3zg**), protected indoles (**3la**, **3lh**) or benzothiophene (**3a$_2$g**) were found to be compatible with the enantioselective protocol - even though slightly diminished *er* were obtained. Finally, an appreciable level of diastereocontrol was achieved by the chiral catalyst for a substrate bearing a menthol unit at the *para* position (**3b$_2$a**). The absolute configuration of all compounds was assigned by analogy with that of **3ja** for which we obtained an X-ray analysis. Unlike for the geometrically constrained **3wa** and (*E*)-**5ab**, the molecular structure revealed a sp^2 hybridized boron atom devoid of an interaction with the amide function, an observation in line with ^{11}B NMR solution analyses (*vide supra*).

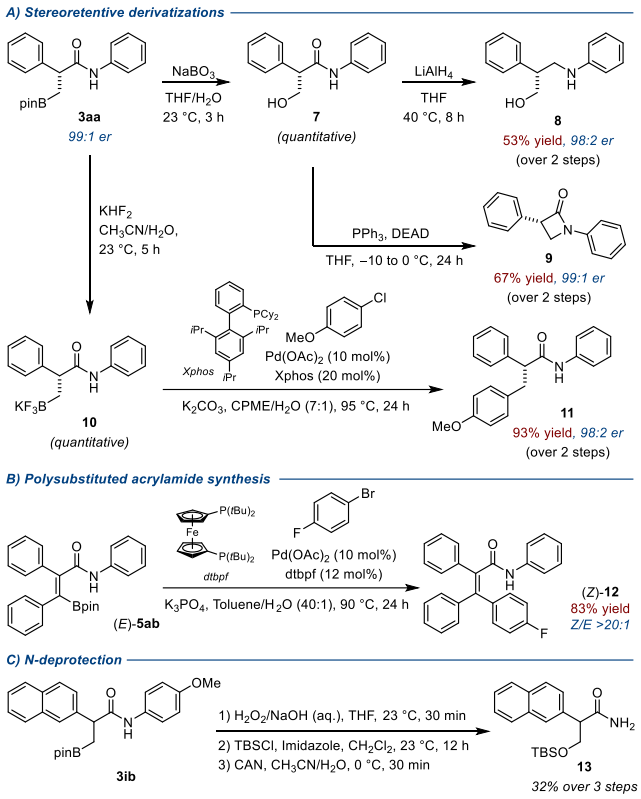


Figure 9. (A) Stereoretentive derivatizations. (B) Synthesis of a polysubstituted acrylamide. (C) Deprotection of the *N*-amide. Yields of isolated product after purification. *Er* determined by HPLC.

The synthetic utility of the Cu-catalyzed borylative carboxamidation of alkenes and alkynes was demonstrated by conducting a series of post-catalytic derivatizations (Figure 9). Organoboron oxidation was performed using sodium perborate hydrate and delivered **7** -a tropicamide analog- quantitatively. Reduction into the corresponding secondary amine **8** demanded forcing conditions and was achieved without noticeable epimerization of the benzylic stereocenter. Starting from **7**, a cyclizative Mitsunobu reaction using diethyl azodicarboxylate (DEAD) and triphenylphosphine afforded β-lactam **9** in 63% yield with preservation of the initial enantiomeric ratio.[29] Attempts to engage **3aa** in Pd-catalyzed Suzuki cross-coupling reactions with various electrophilic partners were unsuccessful. Conversion into the corresponding trifluoro-potassium borate analog **10** enabled to circumvent this problem by applying subsequently the protocol reported by Molander for the Csp^2-Csp^3 coupling of β-trifluoroboratoamide.[30] Thus, 4-chloroanisole was efficiently coupled with **10** using Xphos as supporting ligand and gave **11** in excellent yield without epimerization. The β-borylated acrylamide (*E*)-**5ab** was also efficiently engaged in a Csp^2-Csp^2 Suzuki cross-coupling reaction using 1-bromo-4-fluorobenzene, K_3PO_4 as base and a catalytic combination of $Pd(OAc)_2$ and dtbpf (1,1′-bis(di-*tert*-butylphosphino)-ferrocene).[31] The corresponding acrylamide (*Z*)-**12**, characterized by a tetrasubstituted alkene, was obtained in 83% yield with perfect retention of the initial C=C bond geometry. Finally, deprotection of the *para* methoxyphenyl amide **3ib** was accomplished using cerium ammonium nitrate after alkali oxidation of the (pinacolato)boron unit and subsequent silyl protection using TBS-Cl.

■ CONCLUSION

Starting from readily available vinylarenes and isocyanates, the Cu-catalyzed borylative carboxamidation described in this study provides a direct and practical approach for the construction of α-chiral secondary amides bearing a β-boronate handle. An air-stable [(NHC)Cu] complex is used as precatalyst in its non-enantioselective variant. The method displays broad functional group tolerance and can also be applied to 1,3-dienes, activated bicyclic alkenes and alkynes. An enantioselective Cu-catalyzed borylative carboxamidation of (hetero)vinyl arenes has been developed successfully using a chiral phosphanamine ligand. Direct Hammett correlations were obtained with the enantiomeric ratio of the products by varying the electronic properties of the electrophilic component of the reaction. In contrast, a zero-slope linear correlation was observed with the styrene derivatives, suggesting that enantioselectivity is more sensitive to changes in the structure of the isocyanate than to the structure of styrene. We demonstrated that excellent levels of stereocontrol can be achieved when the particularly electron-deficient 4-bromophenyl isocyanate is employed. We believe the highly selective asymmetric variant of the transformation presented in this study holds promise for devising new strategies to enantioselectively forge amide bonds. The utility of our protocol was further demonstrated in a series of stereoretentive post-functionalizations. Current efforts are directed towards extending the scope of this transformation to unactivated alkenes as well as getting a deeper understanding of the factors that do govern reactivity and selectivity in this reaction.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of all new compounds, spectroscopic, spectrometric and X-ray data for compounds **3wa**; (*E*)-**5ab**; **3ja** (CCDC 1914320-1914322) This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*clement.mazet@unige.ch

Notes

The authors declare no competing financial interest.

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