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Titanium-Promoted Cross-Coupling for the Selective Synthesis of Polysubstituted, Conjugated Amides

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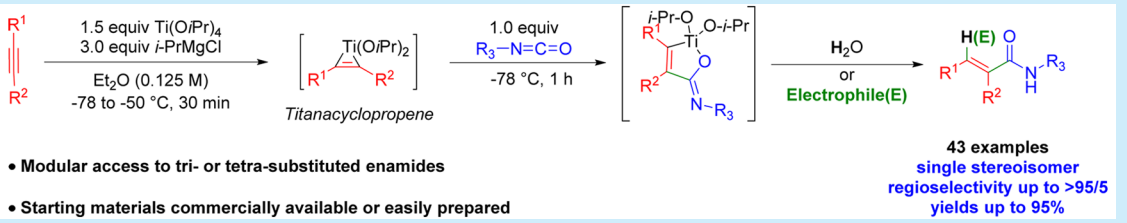
Supporting Information



ABSTRACT: α,β-Unsaturated amides are important building blocks and are key structural elements in a number of biologically active natural products. Despite their importance and prevalence, few methods exist to prepare conjugated amides directly and modularly. To address this gap, a titanium-promoted coupling of alkynes and isocyanates has been developed. The method is highly stereoselective, producing only the *E* isomer with good chemoselectivity and regioselectivity (>95/5), for unsymmetrical internal alkynes that contain a steric bias. The reactive titanacyclopentene intermediate formed from the coupling of the alkyne and isocyanate was additionally reacted with various electrophiles to access tetrasubstituted enamides.

Amides are a common structural motif in drugs, and currently amide bond formation is one of the most common reactions performed in the pharmaceutical industry.[1] Despite the importance of amides in drug discovery, this functional group is typically only formed through the dehydrative condensation of a carboxylic acid and amine utilizing a coupling reagent. While this process is robust, there is a need for new methods that are more environmentally friendly[2] and can readily generate complex, hindered, and/or electron-deficient amides.[3] As such, there have been investigations to address some of these issues, a notable example being the use of arylboronic acids as catalysts.[4] This has also spurred the development of new amide-forming reactions[5] through new mechanistic approaches, such as Danishefsky's use of isonitriles,[6] Rovis' carbene-catalyzed relay coupling between amines and α-reducible aldehydes,[7] and Bode's ketoacid−hydroxylamine ligation.[8] Examples that caught our attention were the rhodium-catalyzed additions of arylboronic acids[9] and -stannanes[10] to isocyanates and the addition of sterically hindered Grignard reagents to sterically hindered isocyanates by Bode.[11] Based on these precedents, it was conjectured that isocyanates can undergo a titanium promoted coupling with alkynes, alkenes, allenes, or imines to form complex amides directly.

Conjugated amides are found in biologically active natural products such as lobatamide C,[12] muironolide A,[13] aplysamine 6,[14] and mirabilin.[15] They are also key building blocks used in the preparation of polymers and biologically active compounds. α,β-Unsaturated amides are versatile building blocks that have been utilized in radical additions,[16] pericyclic reactions,[17] asymmetric hydrogenation,[18] asymmetric conjugate additions,[19] asymmetric epoxidation,[20] and transition-metal-mediated reactions.[21] Despite the importance and utility of α,β-unsaturated amides, methods to prepare this functional group directly are limited. Of the few methods to prepare conjugated amides, most have focused on disubstituted α,β-unsaturated amides using traditional Wittig, Horner−Wadsworth−Emmons,[22] and Peterson[23] olefination reactions with a more recent advance being cross-metathesis.[24] A majority of the methods to prepare disubstituted α,β-unsaturated amides have been directed toward α-branched acrylamides[25] and α,β,γ,δ-unsaturated amides.[26] Methods to prepare tri- and tetrasubstituted α,β-unsaturated amides directly and selectively are severely lacking.[27] Approaches to this class of conjugated amides that have been developed are amino-carbonylation[28] and hydrocarbamoylation[29] of alkynes and rearrangements of propargyl alcohols.[30] While these new approaches have enabled the synthesis of trisubstituted α,β-unsaturated amides, issues still exist such as obtaining high regioselectivity with unsymmetrical internal alkynes and/or the ease with which the substituents can be interchanged.

We sought to address this gap by expanding upon our recent titanium-promoted coupling of alkynes and Weinreb amides to prepare (*E*)-trisubstituted enones selectively.[31] Using this as a starting point, we began optimization of the alkyne−isocyanate coupling (Table 1) by reduction of $Ti(O\text{-}i\text{-}Pr)_4$ in the presence of 4-octyne to generate a titanacyclopropene followed by addition of phenyl isocyanate. It was determined that higher yields were obtained when a slight excess of $Ti(O\text{-}i\text{-}Pr)_4$ was reduced with isopropylmagnesium chloride in a 1:2 ratio (entry 2). The temperature of the reaction mixture upon addition of the isocyanate had a dramatic effect on the efficiency of the reaction.

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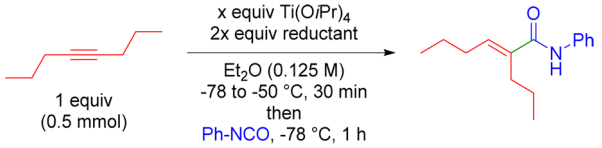
Table 1. Optimization of a Titanium Alkyne Isocyanate Coupling



entry	$Ti(O\text{-}i\text{-}Pr)_4$ (equiv)	reductant (equiv)	PhNCO (equiv)	yield[a] (%)
1	1.1	*i*-PrMgCl (2.2)	1.0	38
2	1.5	*i*-PrMgCl (3.0)	1.0	63
3	1.5	*i*-PrMgCl (3.0)	0.8	62
4	1.5	*i*-PrMgCl (3.0)	1.2	53
5	1.5	*i*-PrMgCl (3.0)	2.0	43
6	1.5	*c*-C_5H_9MgBr (3.0)	1.0	46
7	1.5	*n*-BuLi (3.0)	1.0	7
8[b]	1.5	*i*-PrMgCl (3.0)	1.0	6
9[c]	1.5	*i*-PrMgCl (3.0)	1.0	10
10[d]	1.5	*i*-PrMgCl (3.0)	1.0	49

[a]Isolated yield after flash chromatography. [b]In THF. [c]In 1,4-dioxane. [d]In toluene.

Little to no desired enamide was obtained if phenyl isocyanate was added at −50 °C or above. At these temperatures, the magnesium isopropoxide byproduct preferentially reacted with the isocyanate to form a carbamate. Selective reaction of the isocyanate with the in situ generated titanacyclopropene could be accomplished when the reaction mixture was cooled to −78 °C. Decreasing the concentration of the isocyanate to 0.8 equiv had no effect, whereas increasing its concentration to 1.2 equiv lowered the yield (entries 3 and 4). The standard solvents employed in titanium reductive couplings were screened (Et_2O, THF, 1,4-dioxane, and toluene) with Et_2O producing the highest yield.

Substrate screening was initiated to determine the scope of this coupling reaction under the optimized conditions. First, we examined what effect the sterics of the isocyanate had on the coupling with symmetrical alkynes, diphenylacetylene, and 4-octyne. Higher yields were typically obtained with diphenylacetylene versus 4-octyne, where undesired reductive couplings and decomposition of the titanacycle occurred.[32] Simple phenyl isocyanate (Scheme 1, **1** and **6**) and sterically larger 1-naphthyl isocyanate (**7**) reacted well, whereas 2,6-disubstituted phenyl isocyanates inhibited the coupling, affording the conjugated amide in low yields (**4**, **5**, and **10**). Sterically congested aliphatic isocyanates produced the amides in good yields (**3** and **9**), but the steric bulk of the adamantyl isocyanate did inhibit the rate of the reaction requiring prolonged reaction times for complete conversion to the product. In the case of substrate **9**, the increased reaction time led to decreased yield due to decomposition of the titanacyclopropene, which is corroborated by amide **14** being afforded in higher yield. From here, the regioselectivity of the reaction was examined with unsymmetrical alkynes. In our prior enone synthesis method, it was determined that regioselectivity was based on the steric difference between the substituents on the unsymmetrical alkyne regardless of Weinreb amide employed. That was found not to be the case for the titanium-promoted coupling of unsymmetrical alkynes with isocyanates. In this system, the regioselectivity was based on a synergistic steric interaction between the larger alkyne substituent and the isocyanate. It was determined that for high regioselectivity the steric element of the isocyanate needed to be distal. Coupling of phenyl isocyanate with 1-phenyl-1-propyne afforded amide **11** with a 75:25 regioselectivity, favoring bond formation on the side of the alkyne with the smaller substituent. Simply changing to benzyl isocyanate, pushing the phenyl group away by one carbon, afforded conjugated amide **12** as a single regioisomer. To probe this further, 2-isocyanato-5-methyl-1,1′-biphenyl was prepared, and as speculated, the addition of a substituent ortho to the isocyanate induced a steric interaction yielding **13** as a single regioisomer. Moving the substituent to the meta position only had a minor positive effect (**15** vs **17** and **31** vs **32**).

The system demonstrated complete regioselectivity with 1-phenyl-2-*tert*-butylacetylene (**14**) favoring bond formation α to the phenyl group opposite to 1-phenyl-1-propyne, demonstrating that selectivity is biased toward steric hindrance rather than electronic effects. Trimethylsilylalkynes showed moderate selectivity, presumably due to the longer silicon−carbon bonds, decreasing the steric hindrance in the formation of the titanacyclopropene. To compensate, the TMS was changed to the sterically larger TBS, which increased the regioselectivity (**19** vs **20**). On the basis of this result, a variety of TBS-protected propargyl alcohols were screened (**24**−**28**). By placing the steric element farther away from the alkyne, a single regioisomer was formed regardless of the other alkyne substituent or the isocyanate employed, even with a small aliphatic chain isocyanate (**27**). The yields for amides **28** and **29** were low due to incomplete conversion of the alkyne to the titanacyclopropene.

The stereoselectivity of the reaction was excellent, with every α,β-unsaturated amide prepared having an *E*-configuration. The system had high functional group compatibility, tolerating aromatic and primary aliphatic halides (I, Br, Cl), primary tosylate, silyl ethers, ethers, esters, nitriles, alkenes, a furan, and a pyridine. Due to the poor solubility of 3-isocyanatopyridine in ether, this coupling was performed in a dual solvent system (Et_2O/THF). While the THF cosolvent solubilized the 3-isocyanatopyridine, it also contributed to the lower yield of **26**. Chiral, nonracemic amides **33** and **34** were efficiently prepared from chiral isocyanates with no loss of enantiomeric purity. Of note is that an isothiocyanate could also be employed with no modification to the system, efficiently affording the conjugated thioamide (**35**).

To access tetrasubstituted α,β-unsaturated amides, the addition of a second electrophile was examined. The 5-membered ring titanacycle was quenched with D_2O to afford the β-deuterated conjugated amide (**36**) in 83% yield with greater than 95% deuterium incorporation. The titanacycle could be brominated to afford the vinylic bromide (**37**), a useful handle for further diversification. Additionally, the remaining titanium−carbon bond could be fluorinated, enabling access to β-fluorinated conjugated amide building blocks (**38**). The addition of allyl bromide produced a mixture of C- and N-alkylation products, but the use of a stoichiometric amount of CuO-*t*-Bu in combination with the allyl bromide solely afforded the skipped diene (**39**). An aldehyde did not give rise to an allylic alcohol but rather formed a butenolide (**41**−**43**).[33]

In summary, titanium-promoted coupling of alkynes and isocyanates enables modular access to tri- and tetrasubstituted enamides. The α,β-unsaturated amides are afforded as a single stereoisomer with high regioselectivity (>95/5) for unsymmetrical internal alkynes when a distal steric element is present on either the isocyanate or alkyne. Application of these amides in dual catalytic radical cross-couplings and in the preparation of natural product mimic libraries is underway.

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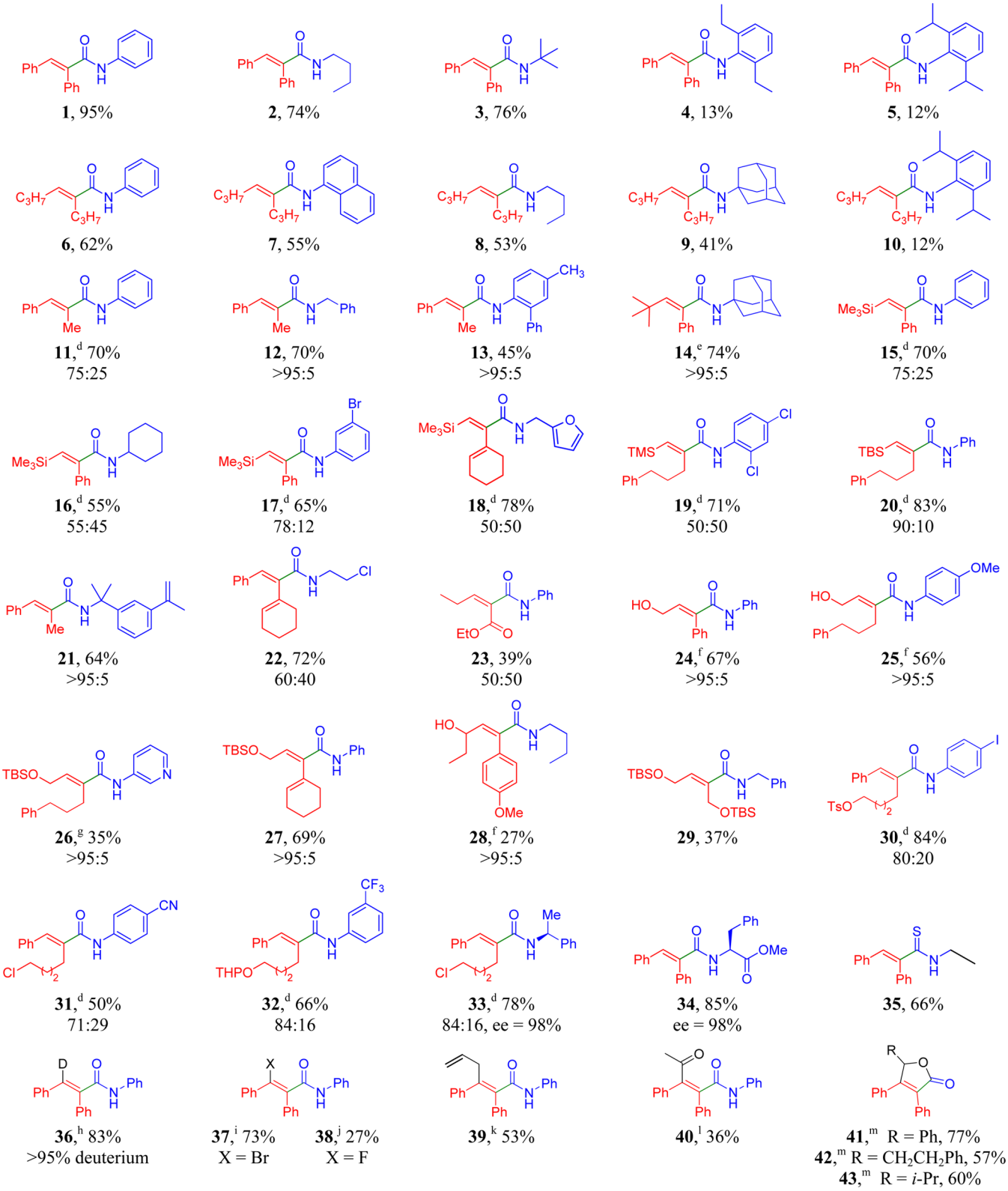
Scheme 1. *α,β*-Unsaturated Amide Substrate Scope,



[a]Conditions: alkyne (0.5 mmol), Ti(O-*i*-Pr)$_4$ (0.75 mmol), *i*-PrMgCl (2.0 M in Et$_2$O, 1.5 mmol), Et$_2$O (4 mL), −78 to −50 °C, 0.5 h, isocyanate (0.5 mmol) at −78 °C for 1 h, addition of H$_2$O. [b]Isolated yields after flash chromatography. [c]Regioisomeric ratios determined by ^{1}H NMR of the crude reaction mixture. [d]Combined isolated yield of regioisomers. [e]Stirred at −78 °C for 12 h after isocyanate addition. [f]Quenched with 3 M HCl. [g]Et$_2$O/THF (1/1) used. [h]Quenched with D$_2$O. [i]2 equiv of NBS. [j]2 equiv of Selectfluor. [k]1 equiv of CuO*t*Bu + 5 equiv of allyl bromide. [l]5 equiv of AcCl. [m]2 equiv of aldehyde.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02537.

Experimental details, product characterization data, and further discussion (PDF)

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Notes

The authors declare no competing financial interest.

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