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Metal-Free Metathesis Reaction of *C*-Chiral Allylic Sulfilimines with Aryl Isocyanates: Construction of Chiral Nonracemic Allylic Isocyanates

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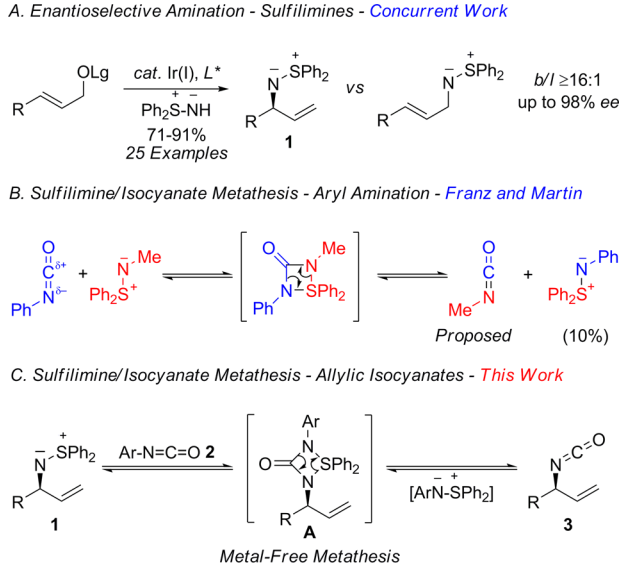
Supporting Information

ABSTRACT: We report the facile and efficient metal-free metathesis reaction of *C*-chiral allylic sulfilimines with aryl isocyanates. This process facilitates the room temperature construction of an array of chiral nonracemic allylic isocyanates, which are versatile intermediates for the construction of unsymmetrical ureas, carbamates, thiocarbamates and amides. Furthermore, the sulfilimine/isocyanate metathesis reaction with 4,4′-methylene diphenyl diisocyanate (4,4′-MDI) circumvents harsh reaction conditions and/or hazardous reagents employed with more classical methods for the preparation of this important functional group.

Isocyanates are important synthetic intermediates in organic chemistry since they provide a convenient precursor to motifs present in materials and bioactive agents, namely, ureas, carbamates, thiocarbamates and amides.[1] For instance, enantiomerically enriched isocyanates have featured in the preparation of drugs for the treatment of cystic fibrosis, Alzheimer's disease and influenza.[2] Nevertheless, despite the importance of this functionality, the asymmetric synthesis of *allylic* isocyanates has not been well developed and relies on classical methods that have a number of inherent limitations.[3−5] For example, the stereoselective [3,3]-rearrangement of an allylic cyanate derived from the corresponding primary allylic carbamate provides an excellent method for the preparation of chiral nonracemic allylic isocyanates, albeit this approach tends to rely on chiral auxiliaries and chiral pool intermediates.[3] Alternatively, the stereospecific Curtius rearrangement of allylic β,γ-unsaturated carboxylic acids, which are themselves preparatively challenging intermediates, provides the allylic isocyanates *via* the acyl azide intermediate without the concomitant [3,3]-rearrangement.[4] Nevertheless, the most direct method for the construction of allylic isocyanates is the treatment of the corresponding allylic amine with phosgene or a suitable equivalent, which requires the use of toxic and expensive reagents, respectively.[5] Hence, the inherent utility of enantiomerically enriched allylic isocyanates coupled with the challenges associated with their preparation makes the development of a more practical method both important and timely.[6]

Recent advances in the metal-catalyzed asymmetric allylic amination reaction with aza-ylides provided the impetus for the following study.[7] We reasoned that *C*-chiral *N*-allylic sulfilimines, which are readily available *via* the asymmetric iridium-catalyzed allylic amination (Scheme 1A), would permit the development of a metal-free metathesis reaction with an aryl isocyanate to afford the corresponding chiral nonracemic allylic isocyanates.[8,9] Although Franz and Martin described the sulfilimine/isocyanate metathesis reaction of *N*-methyl sulfilimine with phenyl isocyanate, the methyl isocyanate adduct central to our hypothesis was not isolated and characterized (Scheme 1B).[10−12] We recognized that the ability to control the fragmentation of the putative four-centered intermediate **A** would be a key component to the efficient synthesis of allylic isocyanates *via* this type of process (Scheme 1C). For example, there are two modes of fragmentation of **A**, which can either generate the desired allylic isocyanate **3** or regenerate the allylic sulfilimine **1**. Notwithstanding this challenge, we envisioned the ability to utilize commercially available and inexpensive aryl isocyanates, which are generally less toxic and expensive than phosgene and the various phosgene equivalents, would provide an attractive approach to this important functionality. Herein, we now describe the

Scheme 1. Inspiration for the Development of the Metal-Free Sulfilimine/Isocyanate Metathesis for the Construction of Allylic Isocyanates

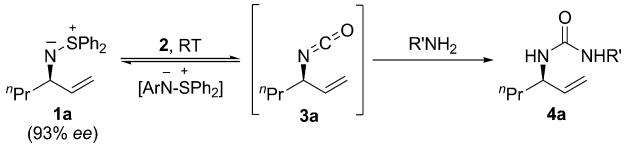


Received: May 8, 2014
Published: August 11, 2014

   dx.doi.org/10.1021/ja504631v | J. Am. Chem. Soc. 2014, 136, 11870−11873

sulfilimine/isocyanate metathesis reaction of enantiomerically enriched allylic sulfilimines **1** with aryl isocyanates **2** for the construction of chiral nonracemic allylic isocyanates **3** (Scheme 1C).

Table 1. Optimization of the Metal-Free Metathesis of *C*-Chiral Allylic Sulfilimines with Aryl Isocyanates for the Construction of *N,N′*-Disubstituted Ureas (R′ = 2-MeOC$_6$H$_4$CH$_2$)[a]



entry	aryl isocyanate 2		equiv of 2	solvent	yield of 4a (%)[b]	*cee* of 4a (%)[c]
1	PIC	**a**	1.0	$CHCl_3$	57	97
2	1-NIC	**b**	"	"	61	100
3	1,4-PDI	**c**	0.5	"	37	99
4	4,4′-MDI	**d**	"	"	67	100
5	PMDI	**e**	0.37	"	57	"
6	4,4′-MDI	**d**	0.5	"	11[d]	"
7	"	"	"	PhMe	53	100
8	"	"	"	THF	54	"
9	"	"	"	DCE	72	"
10	***4,4′-MDI***	***d***	***1.5***	***DCE***	***89***[e]	***100***

[a]All reactions were performed on a 0.175 mmol reaction scale at room temperature for *ca.* 1 h and then quenched with 2-methoxybenzylamine (1 equiv). [b]Isolated yields of the *N*-2-methoxybenzyl urea adduct. [c]The enantiomeric excess was determined by chiral HPLC on the *N*-2-methoxybenzyl urea derivative. [d]Reaction stirred for *ca.* 24 h. [e]Quenched with 2-methoxybenzylamine (3 equiv).

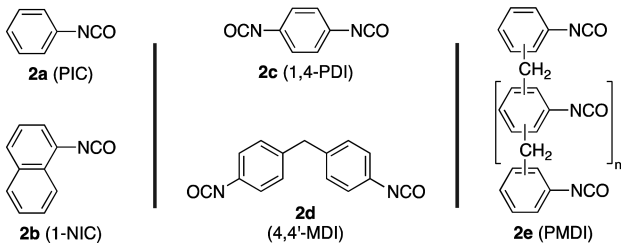


Figure 1. Classes of aryl isocyanates screened in the metal-free metathesis reaction of chiral nonracemic allylic sulfilimines.

Table 1 outlines the optimization of the metal-free metathesis reaction of enantiomerically enriched allylic sulfilimines with aryl isocyanates. Treatment of the sulfilimine **1a** with phenyl isocyanate (PIC) (**2a**) (Figure 1) in chloroform at room temperature furnished the allylic isocyanate **3a**, which was trapped *in situ* with 2-methoxybenzylamine to afford the allylic urea **4a** in 57% yield with excellent chirality transfer but incomplete conversion (entry 1).[13] In order to investigate the influence of the relative stabilities of the isocyanate components (**2** *vs* **3**), 1-naphthyl isocyanate (1-NIC) (**2b**) (ΔH°_{form} = −2.3 kcal/mol) which is considerably less stable than the corresponding PIC (**2a**) (ΔH°_{form} = −16.1 kcal/mol),[14] was examined. Interestingly, this provided only a very minor improvement in the conversion (entry 2), which we attribute to the concomitant destabilization of the aryl sulfilimine product. Additional studies focused on the examination of polysubstituted aryl isocyanates, in which 4,4′-methylene diphenyl diisocyanate (4,4′-MDI) (**2d**) proved superior to 1,4-phenylene diisocyanate (1,4-PDI) (**2c**) and the polymeric aryl isocyanate (PMDI) **2e** (entry 4 *vs* 3/5). Importantly, 4,4′-MDI (**2d**) is inexpensive and one of the least toxic commercially available aryl isocyanates.[15,16] Nevertheless, the allylic isocyanate **3a** is particularly sensitive, since exposure to the aryl isocyanate **2d** for an extended time led to a significantly lower recovery of the urea **4a** (entry 6). Further studies focused on the effect of solvent, in which 1,2-dichloroethane provided a modest improvement in the yield (entry 9 *vs* 7/8). At this juncture, we envisioned that improving the overall efficiency would require increasing the amount of the aryl isocyanate to drive the equilibrium in an analogous manner to the metal-catalyzed crossed metathesis reaction of alkenes.[17] Gratifyingly, treatment of the allylic sulfilimine **1a** with excess 4,4′-MDI (**2d**) provided the allylic urea **4a** in 89% overall yield with complete transfer of chirality (100% *cee*).

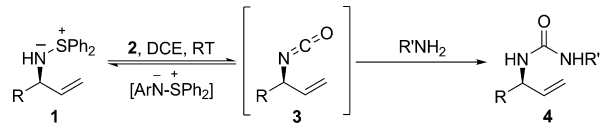
Table 2 outlines the application of the optimized reaction conditions to a range of enantiomerically enriched allylic sulfilimines **1**. Interestingly, the reaction is tolerant of a range of straight chain and branched alkyl derivatives (entries 1−7). Another striking feature with this process is the ability to interchange the aryl isocyanate **2** to assist in the isolation of the allylic urea **4** (entry 1 *vs* 2) and thereby illustrate the versatility of the metathesis reaction. Moreover, this operationally simple process can be conducted on gram scale with similar efficiency (entry 1) and a solution of the allylic isocyanate **3b** was readily isolated in moderate yield *via* distillation (entry 2). Further studies demonstrated that *tert*-butyldimethylsilyl and benzyl protected hydroxyethyl groups, in addition to the tethered *N*-Boc and *N*-Cbz derivatives, provide suitable substrates for this process to afford the formally differentially protected amino alcohols and diamines (entries 8−11). Finally, the chloro-substituted allylic sulfilimine **1l** also provides the allylic urea **4l** to illustrate the mild nature of this process. Overall, this study highlights the synthetic versatility of the metal-free metathesis of allylic sulfilimines to provide allylic ureas **4** in excellent yield without significant racemization of the inherent stereogenic center.

Having established general reaction conditions for the construction of unsymmetrical chiral nonracemic *N,N′*-disubstituted allylic ureas **4**, we elected to examine a range of other useful pronucleophiles, as outlined in Table 3. In this context, we explored primary, secondary and aryl amines to provide the corresponding allylic ureas **4ab**−**4ad**, albeit the aryl amine is slightly less efficient (entries 1−3). Additionally, we also demonstrated alcohols and thiols provide the carbamates and thiocarbamates **4ae**−**4ah** in 78−84% yield without epimerization (entries 4−7). The formation of the carbamate **4ae** is particularly significant, since trapping with aliphatic alcohols proved particularly challenging. Finally, the examination of carbon nucleophiles provided the alkyl and aryl amides in 70−83% yield to illustrate the generality of this approach (entries 8 and 9).

In an effort to extend the synthetic utility of this process, we envisioned the ability to convert the achiral allylic benzoate **5a** directly to the enantioenriched allylic urea **4ab** would provide an attractive synthetic method (Scheme 2). A key and striking feature with this process is the ability to form the reactive allylic isocyanate in the presence of the byproducts from the initial allylic amination to facilitate a challenging one-pot process. Gratifyingly, treatment of the

dx.doi.org/10.1021/ja504631v | *J. Am. Chem. Soc.* 2014, 136, 11870−11873

Table 2. Scope of the Metal-Free Metathesis of *C*-Chiral Allylic Sulfilimines with Aryl Isocyanates for the Construction of *N,N′*-Disubstituted Chiral Nonracemic Allylic Ureas (R′ = 2-MeOC$_6$H$_4$CH$_2$)[a,b,c]



1[d] **4a**[A] 89%, 93% *ee*, 100% *cee*

2[e] **4b**[B] 79%, 96% *ee*, 100% *cee*

3 **4c**[A] 86%, 90% *ee*, 99% *cee*

4 **4d**[A] 90%, 96% *ee*, 100% *cee*

5 **4e**[A] 95%, 97% *ee*, 99% *cee*

6 **4f**[A] 99%, 96% *ee*, 99% *cee*

7 **4g**[A] 93%, 95% *ee*, 99% *cee*

8 **4h**[A] 91%, 87% *ee*, 99% *cee*

9 **4i**[A] 87%, 90% *ee*, 100% *cee*

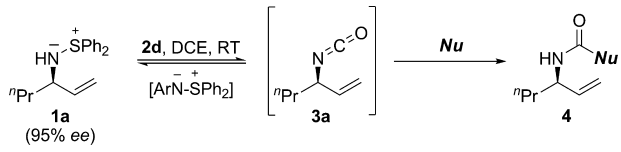
10 **4j**[B] 88%, 93% *ee*, 100% *cee*

11 **4k**[B] 90%, 92% *ee*, 100% *cee*

12 **4l**[A] 84%, 91% *ee*, 99% *cee*

[a]All reactions were carried out on a 0.175 mmol reaction scale in DCE (0.6 M) with the aryl isocyanate **2a** or **2d** at room temperature and then quenched with 2-methoxybenzylamine (3 equiv). [A]Method A: 1.5 equiv of 4,4′-MDI (**2d**). [B]Method B: 3.0 equiv. PIC (**2a**). [b]Isolated yields of the *N*-2-methoxybenzyl urea derivative. [c]Enantioselectivity was determined by chiral HPLC on the *N*-2-methoxybenzyl urea derivative. [d]93% Yield with 100% *cee* on 1 g scale. [e]The intermediary allylic isocyanate **3a** was also distilled and trapped with 1.05 equiv of 2-methoxybenzylamine (see Supporting Information for details).

Table 3. Scope of the Nucleophilic Trapping of the Enantiomerically Enriched Allylic Isocyanates Formed *via* the Metal-Free Metathesis of *C*-Chiral Allylic Sulfilimines with Aryl Isocyanates[a,b,c]



1 **4ab**[d] 92%, 98% *cee*

2 **4ac**[d] 94%, 97% *cee*[e]

3 **4ad**[d] 76%, 97% *cee*

4 **4ae**[f] 78%, 99% *cee*

5 **4af**[g] 84%, 100% *cee*[h]

6 **4ag**[i] 82%, 99% *cee*[h]

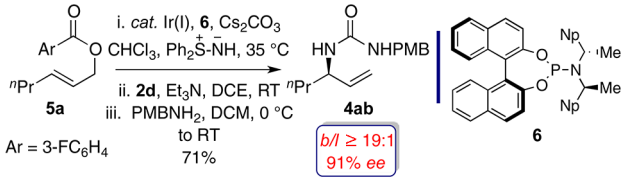
7 **4ah**[i] 82%, 100% *cee*[h]

8 **4ai**[j] 70%, 97% *cee*[e]

9 **4aj**[k] 83%, 100% *cee*

[a]All reactions were carried out on a 0.175 mmol reaction scale in DCE (0.6 M) with 4,4′-MDI (**2d**) at room temperature and then quenched with the respective nucleophile. [b]Isolated yields. [c]Enantiomeric excess was determined by chiral HPLC. [d]Quenched with amine (3 equiv). [e]Enantiomeric excess was determined by chiral HPLC analysis of the *N*-benzyl derivative. [f]Quenched with aliphatic alcohol (6 equiv). [g]Quenched with phenol (3.3 equiv). [h]Enantioselectivity was determined by chiral HPLC analysis of the *N*-2-methoxybenzyl urea derivative. [i]Quenched with thiol (3 equiv). [j]Quenched with Me$_3$Al (12 equiv). [k]Quenched with PhMgBr (3.3 equiv).

Scheme 2. One-Pot Enantioselective Construction of a *N,N′*-Disubstituted Urea *via* the Chiral Nonracemic Allylic Isocyanate Derived from the Allylic Substitution/ Sulfilimine-Isocyanate Metathesis Reaction



allylic benzoate **5a** with *S,S*-diphenylsulfilimine and the chiral iridium complex derived from [Ir(cod)Cl]$_2$ and the phosphoramidite ligand **6**[18] in chloroform at 35 °C furnished the sulfilimine **2a**, which was treated *in situ* with 4,4′-MDI (**2d**) followed by 4-methoxybenzylamine to afford the enantiomerically enriched allylic urea **4ab** in 71% overall yield with excellent regio- and enantioselectivity (*rs* ≥19:1, 91% *ee*).

In conclusion, we have developed a facile and efficient metal-free metathesis reaction of *C*-chiral allylic sulfilimines for the construction of chiral nonracemic allylic isocyanates, which can be trapped with an array of pronucleophiles to facilitate the construction of unsymmetrical ureas, carbamates, thiocarbamates and amides. Furthermore, the sulfilimine/ isocyanate metathesis reaction with 4,4′-methylene diphenyl diisocyanate (4,4′-MDI) circumvents harsh reaction conditions and/or hazardous reagents employed with more classical methods for the preparation of this important motif. Finally, the direct conversion of an achiral allylic alcohol derivative to the corresponding chiral nonracemic allylic urea avoids the challenges associated with the direct allylic alkylation with sodium isocyanate.[8] Hence, we fully anticipate that this transformation will provide a useful alternative to more classical methods for the construction of chiral nonracemic allylic isocyanates, which are important intermediates for materials and medicinal chemistry.

dx.doi.org/10.1021/ja504631v | *J. Am. Chem. Soc.* 2014, 136, 11870−11873

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data and copies of the spectra. 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 sincerely thank the National Sciences and Engineering Research Council (NSERC) for a *Discovery Grant* and Queen's University for generous financial support. NSERC is also thanked for supporting a Tier 1 *Canada Research Chair* (P.A.E.). Additionally, we acknowledge the Royal Society for a *Wolfson Research Merit Award* (P.A.E.).

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(13) For the definition of conservation of enantiomeric excess (*cee*), see: Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

(14) For enthalpies of formation of various isocyanates, see: Selivanov, V. D.; Konstantinov, I. I. *Russ. J. Phys. Ch.* **1975**, *49*, 620. Unfortunately, the corresponding enthalpies of formation of aryl sulfilimines are not available.

(15) *Toxicity:* LC_{50} (inhalation) in male rats for phosgene = 49 mg/m^3 and MDI = 369 mg/m^3. Alternatively, the amount that is immediately dangerous to life or health for phosgene = 8.1 mg/m^3 and MDI = 75 mg/m^3. See: Hazardous Substances Data Bank (http://toxnet.nlm.nih.gov/).

(16) *Cost:* Selected prices for Phosgene = 2.26; Diphosgene = 5.91; PIC = 0.19; 4,4′-MDI = 0.07 ($/g, USD, Aldrich).

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