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Synthesis of α,α-Disubstituted Aryl Amines by Rhodium-Catalyzed Amination of Tertiary Allylic Trichloroacetimidates

Jeffrey S. Arnold, Gregory T. Cizio, and Hien M. Nguyen*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, United States

hien-nguyen@uiowa.edu

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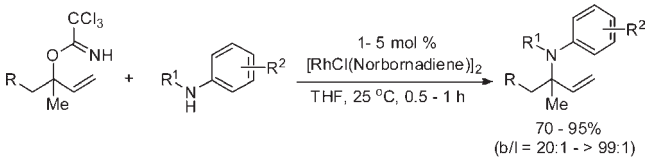
ABSTRACT



The rhodium-catalyzed regioselective amination of tertiary allylic trichloroacetimidates with unactivated aromatic amines is a direct and efficient approach to the preparation of α,α-disubstituted allylic aryl amines in good yield and with excellent regioselectivity. This method is applicable to a variety of unactivated primary and secondary amines and allows for the preparation of reverse prenylated indoles in two steps.

Amines are present in a wide range of natural products, pharmaceutically bioactive drug candidates, materials, and catalysts.[1] Consequently, many practical and elegant routes to the synthesis of amine-containing compounds have been developed.[2] In contrast, approaches for preparation of α,α-disubstituted amines, although important synthetic targets, are limited.[3−5] Transition-metal-catalyzed amination of allylic carbonates or acetates has been utilized to prepare α,α-disubstituted allylic amines.[6,7,9] Palladium catalysts in combination with 1,1-dimethyl-1-propenyl acetate and alkyl amines selectively favor the thermodynamically formed linear products.[6] The branched products, α,α-disubstituted amines, can be formed as the major isomer when DBU (1 equiv) is used to suppress product isomerization. Iridium catalysis of allylic acetates with alkyl amines also provides α,α-disubstituted amines in high yield and regioselectivity.[7] In both palladium[6] and iridium[7] methods, only aniline has been reported as the aryl amine nucleophile.[8] Recently, the iron-catalyzed allylic amination reaction of 1,1-dimethyl-2-propenyl carbonate was reported to work with *para*- and *meta*-substituted anilines, providing the α,α-disubstituted allylic aryl amines in good yield and with excellent levels of regioselectivity.[9] Substituents at the *ortho* position of aniline, however, did not result in the desired allylic amine products.

We recently reported a rhodium-catalyzed regioselective amination of secondary allylic trichloroacetimidates with

(1) For review, see: *Chiral Amine Synthesis*; Nugent, T. C, Ed.; Wiley-VCH: New York, 2008.

(2) Several representative examples: (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. K. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (c) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (e) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810. (f) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (g) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shbasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (h) Clayden, J.; Donnard, M.; Lefrance, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624. (i) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

(3) For diastereoselective and enantioselective nucleophilic addition of organometallic reagents to ketimines, see: (a) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (f) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168.

(4) (a) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243.

(5) There is only one example of palladium-catalyzed enantioselective rearrangement of 3,3-disubstituted allylic trifluoroacetimidates to form 1,1-disubstituted allylic amines, see: (a) Fischer, D. F.; Xin, Z.-Q.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7704. (b) Fischer, D. F.; Barakat, A.; Xin, Z.-Q.; Weiss, M. E.; Peters, R. *Chem.—Eur. J.* **2009**, *15*, 8722.

(6) (a) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17156. (b) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172.

(7) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525.

(8) For recent iridium-catalyzed regio- and enantioselective reaction of primary allylic carbonates with aryl amines to form α-substituted allylic aryl amines, see: Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797.

(9) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053.

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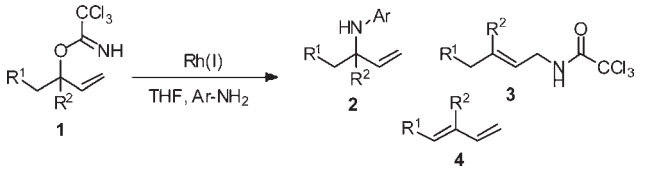
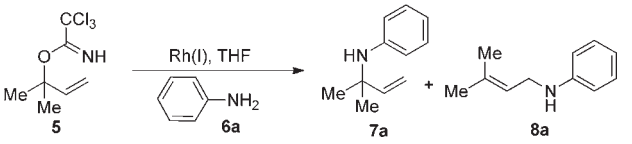


Figure 1. Rh-catalyzed regioselective amination of tertiary allylic trichloroacetimidates.

unactivated anilines.[10,11] Our method is applicable to a wide range of allylic trichloroacetimidates and aromatic amines to provide the branched *N*-arylamines in excellent yields and regioselectivity. With the success of this method, we sought to further investigate our rhodium conditions with tertiary trichloroacetimidates **1** (Figure 1) for the synthesis of α,α-disubstituted aryl amines **2**. An advantage of using branched allylic imidates such as **1** is that they are readily prepared from a variety of ketones and a vinyl Grignard reagent. In addition, the branched substrates react at a faster rate than their corresponding linear isomers because they are less hindered at the olefin unit.[10,12] The potential pitfalls to this approach are that tertiary allylic imidates are prone to undergo Overman rearrangement[13] forming allylic trichloroacetamide **3** (Figure 1) and elimination-forming diene **4** when compared to their secondary allylic counterparts.

We commenced by investigating the amination reaction of tertiary allylic trichloroacetimidate **5** with aniline **6a** (Table 1). Under previous conditions,[10] α,α-disubstituted aryl amine **7a** was isolated in moderate yield and with 14:1 regioselectivity (entry 1). Increasing the catalyst loading improved both yield and regioselectivity (entries 2 and 3). Switching to a more electron-withdrawing phosphite ligand (entry 4), $P(O\text{-}Ph\text{-}F\text{-}4)_3$, improved both yield (69%→86%) and regioselectivity (18:1 → 31:1). Although diene ligands were inefficient in the rhodium-catalyzed regioselective amination reactions with the secondary allylic imidates,[10] cyclooctadiene (COD) and norbornadiene (NBD) rhodium dimers efficiently catalyze the allylic amination of tertiary trichloroacetimidate **5** (entries 5–9) within 30 min to provide α,α-disubstituted aryl amine **7a** in high yield (84%–90%) and regioselectivity (50:1–62:1).

Table 1. Optimization Studies[a]



entry	Rh catalyst	loading (mol %)	temp (°C)	time (h)	yield[b] (%)	**7**/**8**[c] Ratio
1	$RhCl(P(OPh)_3)_3$	2	40	6	45	14:1
2	$RhCl(P(OPh)_3)_3$	4	40	4	60	13:1
3	$RhCl(P(OPh)_3)_3$	10	40	2	69	18:1
4	$RhCl(P(OPh\text{-}F\text{-}4)_3)_3$	10	40	2	86	31:1
5	$[RhCl(COD)]_2$	5	40	0.5	84	54:1
6	$[RhCl(NBD)]_2$[d]	5	40	0.5	89	50:1
7	$[RhCl(NBD)]_2$[d]	5	25	0.5	87	62:1
8	$[RhCl(NBD)]_2$[d]	2.5	25	0.5	90	62:1
9	$[RhCl(NBD)]_2$[d]	1	25	0.5	87	56:1

[a] All reactions were conducted at 0.2 M in THF with 1 equiv of **5** and 3 equiv of **6a**. [b] Isolated yields. [c] The ratio of **7** and **8** was determined by GC in the crude reaction mixture. [d] NBD = Norbornadiene.

Under these conditions, both rearrangement and elimination products (e.g., **3** and **4**, Figure 1) were not observed.[14] Compared to other methods, our approach provides allylic aryl amine **7a** with higher regioselectivity. For instance, reaction of allylic acetate with aniline in the presence of the $[(allyl)PdCl]_2$-$P(OEt)_3$ complex provided **7a** with 4:1 regioselectivity.[6] In another case, reactions of both branched and linear allylic alcohols with aniline in the $Pd(acac)_2$-PPh_3 complex provided linear aryl amine **8a** (Table 1) as the major product.[15]

With optimized reaction conditions in place, the scope of this amination was examined with a wide range of aromatic amines **6b**–**n** (Table 2). Good to excellent yields and regioselectivities were obtained with both electron-donating and -withdrawing 4-substituted anilines (entries 1–4). Allylic aryl amines **6f**–**g** containing *meta*-carbonyl functionality also provided α,α-disubstituted allylic amines **7f**–**g** (entries 5 and 6) in good yield (87% and 84%) and regioselectivity (b/l = 98:1 and >99:1). The amination reaction catalyzed by $[RhCl(NBD)]_2$ is very tolerant of *ortho*-substitution on the aniline nucleophiles (entries 7 and 8), which did not result in allylic aryl amines under iron-catalyzed conditions.[9] This method is also feasible with challenging secondary aniline **6j** (entry 9), and the corresponding allylic amine **7j** was isolated in 85% yield and with 15:1 regioselectivity.

Next, we broadened the scope and showed that tertiary allylic imidates **9**–**12** (Table 3) are suitable substrates under rhodium reaction conditions, generating α,α-disubstituted allylic aryl amines **13**–**16** in good yields and with excellent levels of regioselectivity. It is notable that allylic amination reactions of tertiary imidates **9** and **10** bearing an oxygen substituent at the β-position generally result in

(10) Arnold, J. S.; Stone, R. F.; Nguyen, H. M. *Org. Lett.* **2010**, *12*, 4580.

(11) For other rhodium conditions with secondary allylic carbonates, see: (a) Evans, P. A.; Nelson, J. A. *Tetrahedron Lett.* **1998**, *39*, 1725. (b) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (c) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269.

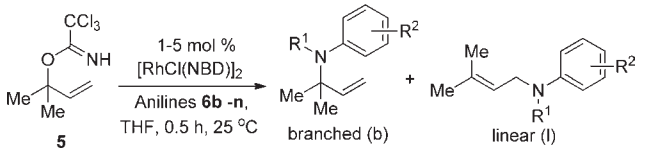
(12) (a) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Org. Chem.* **2002**, 2569. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

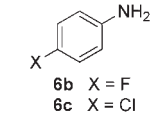
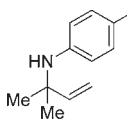
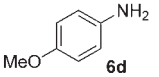
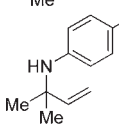
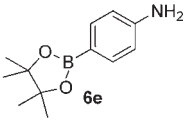
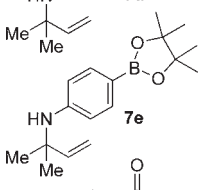
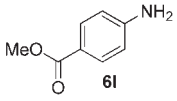
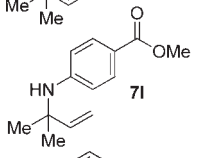
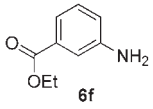
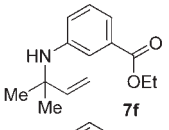
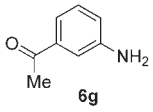
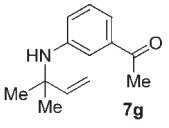
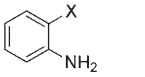
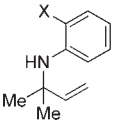
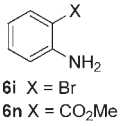
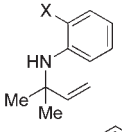
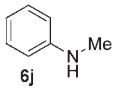
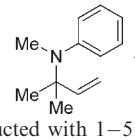
(13) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. (b) For a comprehensive review, see: Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; WILEY-VCH: Weiheim, 2005; Vol. 66, pp 1–107.

(14) Tertiary allylic trichloroacetimidate **5** did slowly undergo the Overman rearrangement to form the undesired trichloroacetamide product (e.g., **3**, Figure 1) upon standing at 25 °C over a period of a few days.

(15) Yang, S. C.; Hsu, Y. C.; Gan, K. H. *Tetrahedron Lett.* **2006**, *62*, 3439–3958.

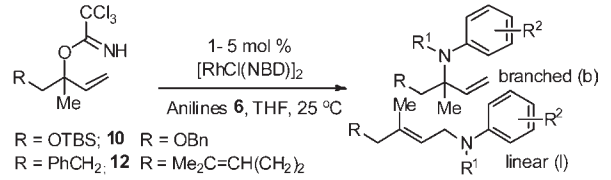
Table 2. Survey of Various Aniline Nucleophiles[a]



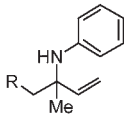
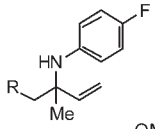
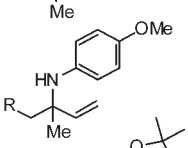
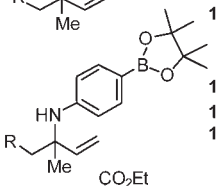
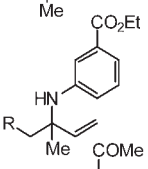
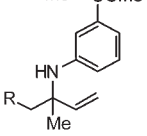
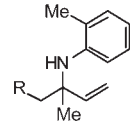
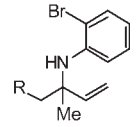
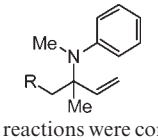
entry	anilines	products	yield(%)[b]	b/l[c]
1	 **6b** X = F **6c** X = Cl	 **7b** X = F **7c** X = Cl	81 85	86:1 >99:1
2	 **6d**	 **7d**	84	66:1
3	 **6e**	 **7e**	77	90:1
4	 **6l**	 **7l**	88	55:1
5	 **6f**	 **7f**	87	98:1
6	 **6g**	 **7g**	84	>99:1
7	 **6h** X = Me **6m** X = isopropyl	 **7h** X = Me **7m** X = isopropyl	95 86	>99:1 34:1
8	 **6i** X = Br **6n** X = CO_2Me	 **7i** X = Br **7n** X = CO_2Me	67 63	24:1 33:1
9	 **6j**	 **7j**	85	15:1

[a] All reactions were conducted with 1−5 mol % $[RhCl(NBD)]_2$ at 0.2 M in THF. [b] Isolated yields. [c] The *b*/*l* ratio was determined by GC.

Table 3. Survey of Tertiary Allylic Trichloroacetimidates[a]



9 R = OTBS; **10** R = OBn
11 R = $PhCH_2$; **12** R = $Me_2C{=}CH(CH_2)_2$

entry	anilines	products	yield(%)[b]	b/l[c]
1	**6a** 	**13a** R = OTBS **14a** R = OBn **15a** R = $PhCH_2$ **16a** R = $Me_2C{=}CHCH_2$	95 90 84 95	>99:1 >99:1 11:1 14:1
2	**6b** 	**13b** R = OTBS **14b** R = OBn **15b** R = $PhCH_2$ **16b** R = $Me_2C{=}CHCH_2$	90 87 96 85	>99:1 >99:1 12:1 18:1
3	**6d** 	**13d** R = OTBS **14d** R = OBn **15d** R = $PhCH_2$ **16d** R = $Me_2C{=}CHCH_2$	92 72 95 73	>99:1 >99:1 12:1 25:1
4	**6e** 	**13e** R = OTBS **14e** R = OBn **16e** R = $Me_2C{=}CHCH_2$	81 63 81	>99:1 >99:1 23:1
5	**6f** 	**13f** R = OTBS **14f** R = OBn **16f** R = $Me_2C{=}CHCH_2$	90 71 93	>99:1 62:1 72:1
6	**6g** 	**13g** R = OTBS **14g** R = OBn **16g** R = $Me_2C{=}CHCH_2$	94 64 95	>99:1 61:1 52:1
7	**6h** 	**13h** R = OTBS **14h** R = OBn	90 88	>99:1 >99:1
8	**6i** 	**13i** R = OTBS **14i** R = OBn	69 95	>99:1 64:1
9	**6j** 	**13j** R = OTBS	78	62:1

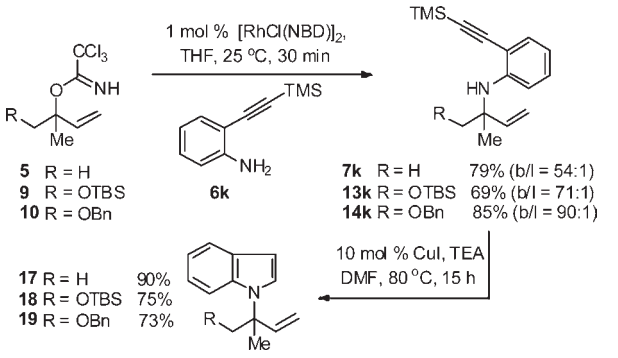
[a] All reactions were conducted at 25 °C at 0.2 M in THF with 1 equiv of allylic imidate and 3 equiv of aniline. [b] Yields are isolated values. [c] The *b*/*l* ratio was determined by GC.

higher regioselectivity compared to tertiary imidates **11** and **12**, suggesting additional chelation control on the metal center. This phenomenon is also observed when comparing the amination reaction of tertiary allylic imidate **9** (Table 3, entry 9) with sterically hindered aniline **6j** to that of 1,1-dimethyl-2-propenyl imidate **5** (Table 2, entry 9), where regioselectivity is 62:1 versus 15:1.

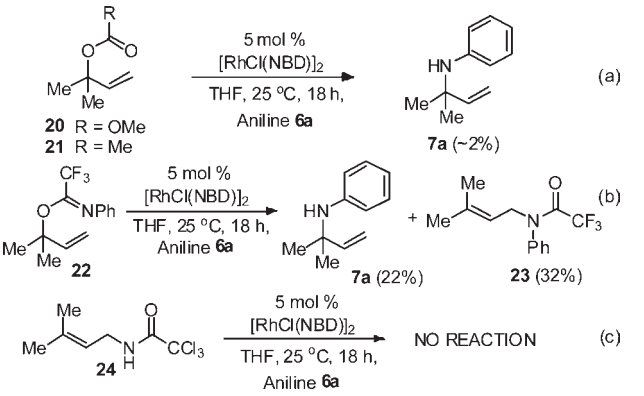
The *N*-1,1-dimethyl-2-propenyl indoles and derivatives are structural motifs found in biologically active natural products.[16] These compounds are commonly prepared via a multistep sequence involving *N*-propargylation of indoline, oxidation to indole, and partial hydrogenation of alkyne to the alkene.[16] Recently, a direct reverse

(16) (a) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628. (c) Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277. (d) Sala, G. D.; Capozzo, D.; Izzo, I.; Giordano, A.; Iommazzo, A.; Spinella, A. *Tetrahedron Lett.* **2002**, *43*, 8839. (e) Sugiyama, H.; Shioiri, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, 3489. (f) Roe, J. M.; Webster, R. A.; Ganesan, A. *Org. Lett.* **2003**, 2825.

Scheme 1. Synthesis of *N*-Isoprenyl Indoles



Scheme 2. Control Experiments



isoprenylation of indole has been described.[17] Transition-metal-catalyzed ring closure of 2-alkynyl anilines could potentially provide access to 1,1-disubstituted indoles;[18] thus we reasoned that allylic amination of tertiary trichloroacetimidates (Scheme 1) in the presence of 2-((trimethylsilyl)ethynyl) aniline and subsequent ring closure would result in an efficient two-step synthesis of varied reverse prenylated indoles. Accordingly, tertiary trichloroacetimidates **5**, **9**, and **10** (Scheme 1) were subjected to optimized amination conditions with aniline **6k** resulting in the allylic aryl amine products **7k**, **13k**, and **14k**, respectively, in good yield (69%−85%) and with excellent levels of regioselectivity (54:1−90:1). The branched aryl amine products subsequently cyclized to the corresponding reverse prenylated indoles **17**, **18**, and **19** (Scheme 1) in high yield after treatment with CuI at 80 °C for 15 h.

It has been proposed that palladium coordinates to both the imidate nitrogen and the double bond of primary allylic trichloroacetimidates to form the corresponding palladium−olefin complex, which is activated toward the nucleophilic attack.[19] It is envisioned that a complementary approach would arise from coordination of a rhodium catalyst to both the nitrogen and the double bond of tertiary allylic imidate to form the activated rhodium−olefin complex. Thus, we decided to verify the unique features of the trichloroacetimidate to potentially act as both the directing group and the leaving group in allylic amination reaction by subjecting both allylic carbonate and acetate **20** and **21** (Scheme 2a) to our reaction conditions. Although the starting materials were completely consumed, less than 2% yield of amination product **7a** was isolated after 18 h. In another control experiment, *N*-phenyl trifluoroacetimidate **22** (Scheme 2b) was subjected to our rhodium conditions which resulted in a 22% yield of branched allylic amine **7a** and 32% of the rearrangement product **23**. These results demonstrate that the strongly coordinating nitrogen atom of the trichloroacetimidate group to the rhodium catalyst is crucial for efficient allylic amination. We also performed a control study with allylic trichloroacetamide **24** (Scheme 2c), which results from Overman rearrangement,[13] to determine if it is an intermediate in the amination reaction. No allylic amine products were observed after 18 h.

In summary, we have developed a rhodium-catalyzed reaction that efficiently facilitates regioselective amination of tertiary allylic trichloroacetimidates with a variety of aromatic amines to provide the desired α,α-disubstituted allylic amines in good yields and with excellent levels of regioselectivity. Application of the procedure to a variety of tertiary allylic imidates and amines, exploration of the possibility of rendering the amination enantioselective, and mechanistic studies of this rhodium-catalyzed amination are underway and will be reported in due course.

Acknowledgment. We thank the University of Iowa for financial support and Robert F. Stone (2010 REU student) for initial studies with tertiary imidates **9** and **10**.

Supporting Information Available. Experimental procedure and full compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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