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Rhodium-Catalyzed Regioselective Amination of Secondary Allylic Trichloroacetimidates with Unactivated Aromatic Amines

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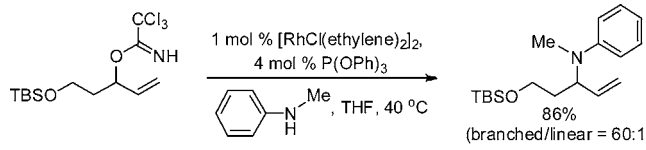
ABSTRACT



The use of unactivated aromatic amines in the rhodium-catalyzed regioselective amination of secondary allylic trichloroacetimidates is explored. The desired *N*-arylamines are obtained in high yields and regioselectivity, favoring the branched amination products. The presence of the trichloroacetimidate leaving group was found to be critical for successful regioselective amination reactions with unactivated aromatic amines. Control studies show that rhodium is not simply acting as a Lewis acid to activate the trichloroacetimidate leaving group.

Allylic *N*-arylamines are important structural motifs found in a variety of biologically important natural and unnatural products.[1] Recently, several approaches to the preparation of *N*-arylamines have been investigated with allylic carbonates and acetates employing transition metal catalysts.[2] The use of palladium catalysts in allylic amination of unsymmetrical allylic acetates with anilines tends to favor the thermodynamic linear product.[2c] The kinetically branched isomer, however, can be formed as the major product when DBU is employed to suppress product isomerization.[2c] The Hartwig group has recently reported an elegant strategy for accessing branched *N*-arylamines with excellent regio- and enantioselectivity via iridium-catalyzed amination of allylic carbonates with unactivated anilines.[2b] This method, however, does not work well with acyclic secondary aromatic amines. The rhodium method reported by Evans is limited to activating and stabilized anionic anilines.[2a] When neutral aromatic amines without an activating group on the nitrogen atom were employed as nucleophiles, the branched *N*-arylamines were isolated in modest yields and regioselectivity.[3]

Given our recent interest in transition-metal-catalyzed reaction methodologies with secondary allylic and glycosyl trichloroacetimidate substrates in carbohydrate synthesis,[4] we investigated a new strategy for the synthesis of *N*-arylamines **2** employing allylic trichloroacetimidates **1** and neutral aromatic amines (Figure 1).[5] A potential problem in this approach is that imidates **1** could undergo the Overman rearrangement to the corresponding products **3**.[6] Herein, we

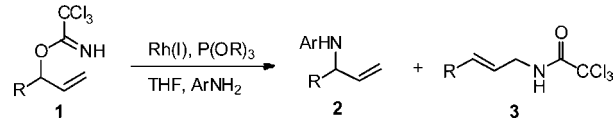


Figure 1. Rh-catalyzed regioselective amination of allylic trichloroacetimidates.

(1) (a) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum: New York, NY, 1975; Vol. 1−5. (b) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) (a) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269. (b) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (c) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172. (d) Takeuchi, R.; Ue, N.; Tanabe, I.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525.

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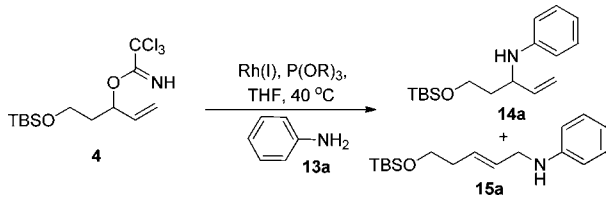
report a complementary rhodium-catalyzed regioselective amination of secondary allylic trichloroacetimidates **1**. In contrast to other known methods,[2a,b] our reaction conditions are feasible with acyclic secondary anilines and α-substituted allylic substrates.

The Rh-catalyzed regioselective amination reaction was optimized by changing the reaction parameters (Table 1).

Table 1. Optimization of Rh-Catalyzed Amination of Allylic Trichloroacetimidate **4** with Aniline **13a**



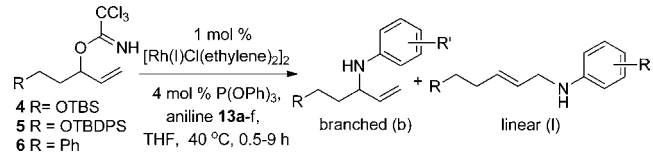
entry	Rh source	Rh (mol %)	$P(OR)_3$	$P(OR)_3$ (mol %)	time (h)	yield[a]	14/15 ratio[b]
1	$RhCl(PPh_3)_3$	10	$P(OMe)_3$	20	24	13%	5:1
2	$[RhCl(cyclooct)_2]_2$	5	$P(OMe)_3$	20	24	37%	4:1
3	$[RhCl(COD)_2]_2$	5	$P(OMe)_3$	20	24	39%	41:1
4	$[RhCl(ethylene)_2]_2$	5	$P(OMe)_3$	20	7	84%	65:1
5	$[RhCl(ethylene)_2]_2$	5	$P(OiPr)_3$	20	24	23%	10:1
6	$[RhCl(ethylene)_2]_2$	5	$P(OPh)_3$	20	0.5	95%	>99:1
7	$[RhCl(ethylene)_2]_2$	2	$P(OPh)_3$	8	0.5	95%	>99:1
8	$[RhCl(ethylene)_2]_2$	1	$P(OPh)_3$	4	0.5	96%	>99:1

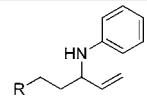
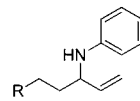
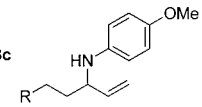
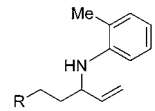
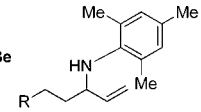
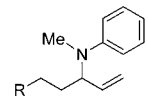
[a] Reported based on GC purity of isolated products. [b] The ratio was determined by GC in the crude reaction mixture.

Utilizing 10 mol % of Wilkinson's catalyst modified with trimethyl phosphite ligand (20 mol %)[3] in the presence of aniline nucleophile **13a** (3 equiv) at 40 °C provided the corresponding *N*-arylamines **14a** and **15a** in a combined 13% yield, with 5:1 regioselectivity favoring the branched product **14a** (entry 1). The branched product **14a** was obtained in higher yield and regioselectivity (65:1) in the presence of 5 mol % of $[RhCl(ethylene)_2]_2$ and 20 mol % of $P(OMe)_3$ (entry 4). The use of a more sterically hindered ligand, $P(OiPr)_3$, was detrimental to the reaction (entry 5), while use of a more electron-withdrawing ligand, $P(OPh)_3$,[7] significantly shortened the reaction time and improved both the yield (84% → 95%) and regioselectivity (65:1 → 99:1) (entry 6). Lowering the metal and ligand loadings further did not diminish the yield or the regioselectivity (entries 7 and 8). Compared to other systems, this chemistry provides the branched product such as **14a** with higher regioselectivity. For instance, reaction of allylic carbonate with **13a** in the presence of Wilkinson's catalyst provided the branched product in poor yield and with 10:1 regioselectivity.[3] Under iridium conditions, reaction of allylic carbonate with **13a** provided the products with 13:1 regioselectivity.[2d]

With the initial optimal conditions in hand, a variety of aniline derivatives **13a**−**f** were investigated with allylic trichloroacetimidates **4**−**6** (Table 2). The branched *N*-

Table 2. Rh-Catalyzed Amination with Anilines **13a**−**f**



	anilines	products		time (h)	yield[a]	ratio (b/l)[b]
1	**13a**		**16a** R = OTBDPS	0.5	94%	>99:1
			17a R = Ph	0.5	97%	>99:1
2	**13b**		**14b** R = OTBS	3.5	96%	>99:1
			16b R = OTBDPS	2	99%	>99:1
			17b R = Ph	0.5	94%	>99:1
3	**13c**		**14c** R = OTBS	9	72%	>99:1
			16c R = OTBDPS	0.5	93%	>99:1
			17c R = Ph	3	93%	>99:1
4	**13d**		**14d** R = OTBS	4	94%	>99:1
			16d R = OTBDPS	4	83%	>99:1
			17d R = Ph	7	80%	>99:1
5	**13e**		**14e** R = OTBS	4	85%	70:1
			16e R = OTBDPS	4[c]	83%[c]	90:1[c]
			17e R = Ph	1[c]	83%[c]	91:1[c]
6	**13f**		**14f** R = OTBS	9	86%	60:1
			16f R = OTBDPS	4[c]	70%[c]	>99:1[c]
			17f R = Ph	1[c]	99%[c]	83:1[c]

[a] Reported based on GC purity of isolated products. [b] The ratio was determined by GC in the crude reaction mixture. [c] 5 mol % Rh and 20 mol % $P(OPh)_3$ at room temperature.

arylamines **14**, **16**, and **17** were obtained in good yield and with excellent regioselectivity. Importantly, the Overman rearrangement products **3** (Figure 1) were not observed in these reactions. The observed reaction time for electron-rich aniline **13c** was longer than more electron-deficient nucleophiles in the allylic amination reaction (entry 2). This is likely due to the binding of rhodium metal to both the nitrogen and oxygen groups of the product **14c**, resulting in slow turnover rates of the rhodium catalyst. The current method is also feasible with sterically hindered anilines **13d**−**f** (entries 4−6). Reaction of **4** with secondary aniline **13f** provided the *N*-arylamine **14f** with 60:1 regioselectivity (entry 6). Under iridium conditions,[2b] reaction of allylic carbonates with secondary anilines such as **13f** provided the products with poor regioselectivities (1:1 → 4:1).

(3) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

(4) (a) Mercer, G. J.; Yang, J.; McKay, M. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2008**, *130*, 11210. (b) Yang, J.; Cooper-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M. *J. Org. Chem.* **2008**, *73*, 794. (c) Mensah, E. A.; Nguyen, H. M. *J. Am. Chem. Soc.* **2009**, *131*, 8778.

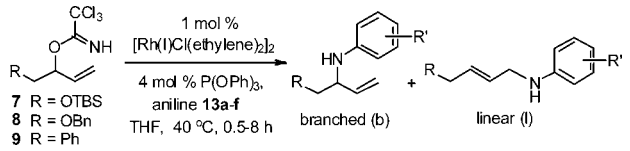
(5) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

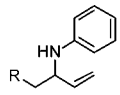
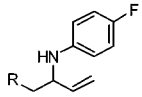
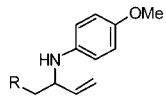
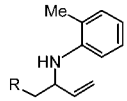
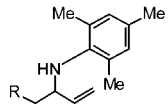
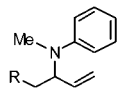
(6) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. For a comprehensive review, see: (b) Overaman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley-VCH: Weiheim, 2005; Vol. 66, pp 1−107.

(7) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

The Rh-catalyzed regioselective allylic amination also works well with β-substituted allylic trichloroacetimidates **7**−**9** (Table 3). In the presence of anilines **13a**−**f**, the desired

Table 3. Rh-Catalyzed Regioselective Amination of β-Substituted Allylic Trichloroacetimidates **7**−**9**



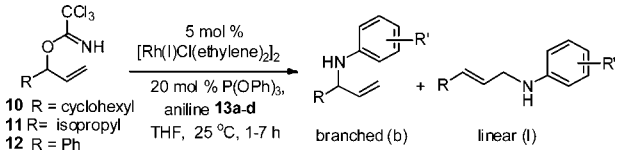
entry	anilines	products		time (h)	yield[a]	ratio (b/l)[b]
1	**13a**		**18a** R = OTBS	1	95%	>99:1
			19a R = OBn	0.5	99%	>99:1
			20a R = Ph	2	94%	>99:1
2	**13b**		**18b** R = OTBS	1	91%	>99:1
			19b R = OBn	0.5	96%	>99:1
			20b R = Ph	2	92%	>99:1
3	**13c**		**18c** R = OTBS	8	20%	>99:1
			19c R = OBn	6	47%	>99:1
			20c R = Ph	2	80%	>99:1
4	**13d**		**18d** R = OTBS	2	94%	>99:1
			19d R = OBn	3	97%	>99:1
			20d R = Ph	3	87%	> 99:1
5	**13e**		**18e** R = OTBS	2	94%	>99:1
			19e R = OBn	3	87%	>99:1
			20e R = Ph	1[c]	93%[c]	80:1[c]
6	**13f**		**18f** R = OTBS	2	94%	>99:1
			19f R = OBn	3	99%	32:1
			20f R = Ph	1[c]	98%[c]	30:1[c]

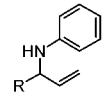
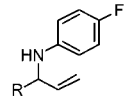
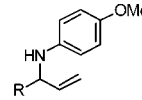
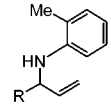
[a] Reported based on GC purity of isolated products. [b] The ratio was determined by GC in the crude reaction mixture. [c] 5 mol % Rh and 20 mol % $P(OPh)_3$ at room temperature.

products **18**−**20** were formed with excellent regioselectivity (entries 1−6). As expected, reaction of **7** and **8**, containing the OTBS and OBn at the β-position, provided the products **18c** and **19c** in much lower yields (entry 3). These results are consistent with what had been observed with substrate **4** (Table 2). Reaction of β-phenyl allylic trichloroacetimidate **9** with sterically demanding anilines **13e**,**f** required higher catalyst loading (entries 5 and 6). Overall, our reaction is more regioselective than other systems.[2a] For instance, reaction of the allylic carbonate derivative of **7** with TolNLi(Mbs) provided the amination product with 23:1 regioselectivity. Similarly, reaction of allylic carbonate derivatives of **8** and **9** provided the amination products with regioselectivity of 8:1 and 20:1, respectively.

Allylic carbonates containing substituents at the α-position with respect to the carbonate leaving group are known to be challenging substrates, and they often provide amination products with poor regioselectivity in favor of linear products.[2a] We found that reactions of α-substituted allylic trichloroacetimidates **10**−**12** with anilines **13a**−**d** in the presence of 5 mol % $[RhCl(ethylene)_2]_2$ and 20 mol % $P(OPh)_3$ at 25 °C provided the branched products **21**−**23** as the major isomers (Table 4). The regioselectivity decreased

Table 4. Rh-Catalyzed Regioselective Amination of α-Substituted Allylic Trichloroacetimidates **10**−**12**



entry	anilines	products		time (h)	yield[a]	ratio (b/l)[b]
1	**13a**		**21a** R = cyclohexyl	4	96%	53:1
			22a R = isopropyl	4	94%	31:1
			23a R = Ph	6	75%	90:1
2	**13b**		**21b** R = cyclohexyl	4	91%	42:1
			22b R = isopropyl	3	94%	36:1
			23b R = Ph	6	85%	19:1
3	**13c**		**21c** R = cyclohexyl	4	93%	42:1
			22c R = isopropyl	4	88%	45:1
			23c R = Ph	1	84%	39:1
4	**13d**		**21d** R = cyclohexyl	4	70%	12:1
			22d R = isopropyl	7	73%	14:1

[a] Reported based on GC purity of isolated products. [b] The ratio was determined by GC in the crude reaction mixture.

as the aniline became more sterically hindered (entry 4). Under the Wilkinson catalyst modified with trimethyl phosphite conditions, reaction of the isopropyl allylic carbonate derivative of **11** with TolNLi(Mbs) provided the linear product as the major isomer.[2a]

Trichloroacetimidate is among the most widely used anomeric leaving groups in carbohydrate chemistry,[8] and it is generally activated with strong and moisture-sensitive Lewis acids such as BF_3-OEt_2,[9] TMSOTf,[10] TBSOTf,[11] and Tf_2O.[12] To determine if rhodium acts as a Lewis acid to activate the trichloroacetimidate group, we investigated reaction of secondary trichloroacetimidate **4** with aniline **13a** in the presence of 2 mol % of BF_3−OEt_2 at 40 °C (Scheme 1). At 15 h, GC analysis showed that the reaction reached

(8) (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Schmidt, R. R.; Jung, K.-H. *Carbohydr. Chem. Biochem.* **2000**, 5. (c) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900.

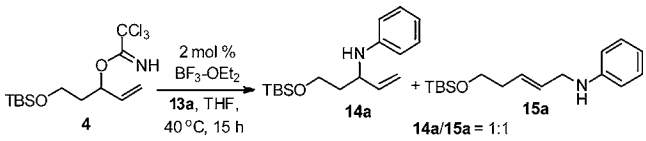
(9) (a) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141. (b) Zimmermann, P.; Bommer, R.; Bär, T.; Schmidt, R. R. *J. Carbohydr. Chem.* **1988**, *7*, 435.

(10) (a) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694. (b) Paulsen, H.; Wilkens, R.; Reck, F.; Brockhausen, I. *Liebigs. Ann. Chem.* **1992**, 1303. (c) Kulkarni, S. S.; Hung, S.-C. *Lett. Org. Chem.* **2005**, *2*, 670.

(11) Haase, W. C.; Seeberger, P. H. *Curr. Org. Chem.* **2000**, *4*, 481.

(12) Dobarro-Rodriguez, A.; Trumtel, M.; Wessel, H. P. *J. Carbohydr. Chem.* **1992**, *11*, 255.

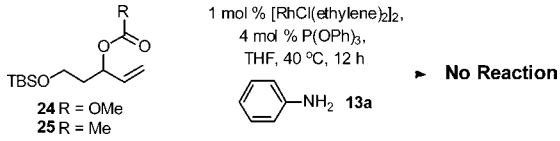
Scheme 1. BF_3-OEt_2-Promoted Allylic Amination Reaction



99% conversion with a 1:1 mixture of the branched product **14a** and the linear product **15a**.[13] This result provides evidence that the rhodium catalyst does not act as a Lewis acid.

To compare the reactivity and efficiency of the allylic trichloroacetimidate with the commonly used allylic acetate and carbonate under our conditions, reactions of allylic methyl carbonate **24** and acetate **25** were attempted with aniline **13a** (Scheme 2). The amination products were not

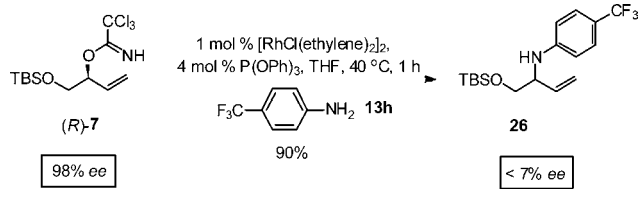
Scheme 2. Control Experiments with Allylic Carbonate **23** and Acetate **24**



observed in these control experiments even if the reactions had been stirring at 40 °C for 12 h, suggesting that both allylic carbonate **24** and acetate **25** were less reactive than secondary allylic trichloroacetimidate **4**.[14]

To clarify the stereochemical outcome of the rhodium-catalyzed amination with allylic trichloroacetimidate and gain insight into the possible mechanism of the reaction, the enantiomerically enriched allylic trichloroacetimidate **7**[15] was subjected to our rhodium reactions in the presence of 4-trifluoromethylaniline **13h** (Scheme 3). The branched

Scheme 3. Rh-Catalyzed Amination of Enantiomerically Enriched Allylic Trichloroacetimidate **7**



product **26** was obtained in 90% yield (branched/linear >99:1) with less than 7% ee. This experiment indicates that the amination reaction proceeds with a significant amount of racemization. Furthermore, this result implies that our rhodium-catalyzed amination reaction with allylic trichloroacetimidates is completely different from other systems such as palladium,[16] molybdenum,[17] iridium,[18] ruthenium,[19] and rhodium with allylic carbonates and activated anilines,[3] whose reactions have been established to proceed with the conservation of stereochemistry in the products.

In summary, a rhodium−phosphite complex is found to be an efficient catalyst for the regioselective amination of secondary allylic trichloroacetimidates with unactivated, neutral primary and secondary anilines to provide *N*-arylamines in high yield and with excellent regioselectivity, favoring the branched products. Our allylic amination reaction is also applicable with acyclic secondary aniline and α-substituted allylic trichloroacetimidates to provide the amination products with high regioselectivity. Distinct from other amination methods where the reaction proceeds with overall retention, our reaction proceeds with a significant amount of racemization. Overall, these unique features make our rhodium-catalyzed amination reaction of secondary allylic trichloroacetimidates a useful method for the development of enantioselective reactions. The mechanistic studies of this allylic amination reaction are underway.

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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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(13) Amination reactions of both primary (*E*)- and (*Z*)-allylic trichloroacetimidates proceeded to completion within 6 h with use of 2 mol % BF_3-OEt_2, and the linear product was obtained as the major isomer.

(14) We also performed the control experiments with both primary (*E*)- and (*Z*)-allylic trichloroacetimidates. The amination products were not observed with use of 1 mol % $[Rh(ethylene)_2Cl]_2$ and 4 mol % $P(OPh)_3$.

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