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Allylpalladium Umpolung in the Three-Component Coupling Synthesis of Homoallylic Amines

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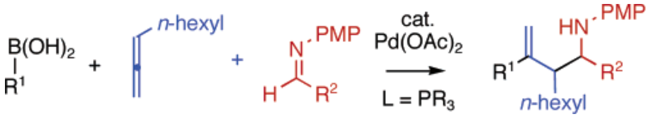
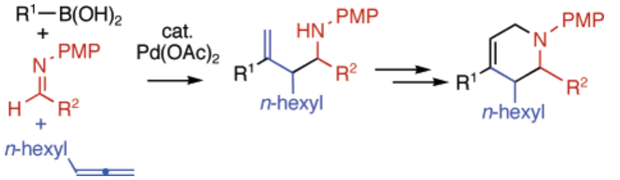
ABSTRACT



Homoallylic amines and α-amino esters were prepared via a Pd(II)-catalyzed coupling of boronic acids and 1,2-nonadiene with ethyl iminoacetate or aliphatic, aromatic, and heteroaromatic imines. The allylpalladium umpolung was induced by a Pd(OAc)$_2$ catalyst with commercial phosphine ligands.

Homoallylic amines serve as building blocks in the construction of biologically relevant heterocycles.[1] Complex syntheses of substituted allylmetal reagents[2] often render the preparation of homoallylic amines via the traditional direct addition of main group allylmetal nucleophiles to imines[3] problematic. Herein (Scheme 1), we report a Pd-catalyzed three-component coupling of organoboronic acids, allenes, and imines providing selectively branched homoallylic amines under mild conditions with excellent regio- and diastereoselectivity, as well as the conversion of the amines into 2,3,4-trisubstituted tetrahydropyridines.[4] The palladium acetate catalyst with commercial monodentate phosphine ligands efficiently induces an in situ umpolung of catalytic electrophilic allylpalladium(II) intermediates, permitting the allyl transfer to imines.[5] In contrast, our previously reported coupling of allenes and allenoates with organoboronic acids and aldehydes[6] required catalysis by allylpalladium(II) complex **1** (Table 1) featuring a “nontransferable” auxiliary allyl ligand.[7] Notably, a Pd-catalyzed In-mediated coupling of aryl iodides, allene (C_3H_4), and imines realizes the allylpalladium umpolung via reductive transmetalation of the allylpalladium intermediate with In metal.[8] Related, but

Scheme 1. Synthetic Strategy



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[1] (a) Pandey, M. K.; Bisai, A.; Pandey, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 5039. (b) Gebauer, J.; Devi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43. (c) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595.

[2] (a) Kabalka, G. W.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 7325. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Panek, J. S.; Yang, M.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003.

[3] (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

[4] Mateeva, N. N.; Winfield, L. L.; Redda, K. K. *Curr. Med. Chem.* **2005**, *12*, 551.

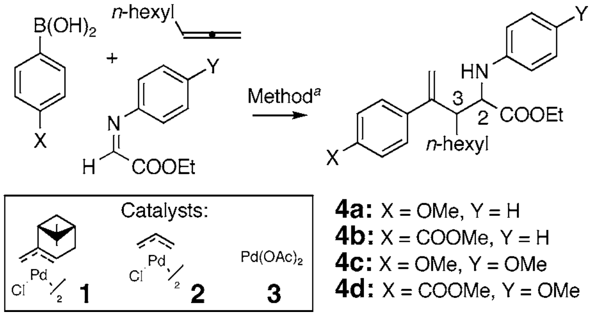
[5] Bis-π-allylpalladium complexes formed in situ via double transmetalation of allylmetal reagents to Pd(II) centers react with electrophiles; see: (a) Szabo, K. J. *Chem.−Eur. J.* **2004**, *10*, 526. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. Mono-π-allylpalladium complexes bearing three-coordinate “pincer” (N−C−N or P−C−P) ligands also react with electrophiles. See: (c) Sebelius, S.; Szabo, K. J. *Eur. J. Org. Chem.* **2005**, 2539. (d) Solin, N.; Kjellgren, J.; Szabo, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026.

[6] (a) Hopkins, C. D.; Guan, L.; Malinakova, H. C. *J. Org. Chem.* **2005**, *70*, 6848. (b) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221.

[7] The utility of catalyst **1** in asymmetric nucleophilic allylation has been demonstrated. See: (a) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.

10.1021/ol0624528 CCC: $33.50

Table 1. Three-Component Coupling to Iminoacetates



entry	catalyst	ligand	product	yield (%)^b	dr
1	**1**	–	**4a**	35	8:1
2	**1**	P(t-Bu)$_3$^{c}	**4a**	53	5:1
3	**1**	P(o-Tol)$_3$	**4a**	61	7:1
4	**2**	–	**4a**	39	4:1
5	**2**	P(o-Tol)$_3$	**4a**	51	8:1
6	**3**	–	**4a**	41	6:1
7	**3**	S-PHOS^d	**4a**	56	6:1
8	**1**	P(t-Bu)$_3$^{c}	**4b**	70	18:1
9	**1**	P(o-Tol)$_3$	**4b**	76	13:1
10	**1**	P(t-Bu)$_3$^{c}	**4c**	36	11:1
11	**1**	P(t-Bu)$_3$^{c}	**4d**	62	13:1
12	**3**	P(t-Bu)$_3$^{c}	**4c**	54	10:1
13	**3**	P(t-Bu)$_3$^{c}	**4d**	74	12:1

[a] Method: boronic acid/allene/imine = 2:5:1 (mol equiv), 10 mol % of Pd catalyst **1**, **2**, or **3**, 10 mol % of ligand L, CsF (4.0 equiv), THF, rt, 24 h. [b] Isolated yields. [c] The ligand was used as its tetrafluoroborate salt HP(t-Bu)$_3$BF$_4$. [d] 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

mechanistically distinct, Ni-catalyzed elaborations of dienes and allenes fail to control the regiochemistry, providing mixtures of branched and linear homoallylic alcohols.[9]

To extend our coupling protocol,[6b] a reaction between *p*-methoxyphenylboronic acid, 1,2-nonadiene, and activated ethyl iminoacetates[10] with various N-protecting groups[11] catalyzed by complexes **1**−**3** was investigated (Table 1). In contrast to our prior work,[6b] commercial allylpalladium complex **2** and Pd(OAc)$_2$ catalyst **3** in the presence of optimum phosphine ligands (P(o-Tol)$_3$ and S-PHOS, Table 1) afforded amine **4a** in surprisingly high yields of 51−56% (entries 4−7, Table 1),[12] competitive with the performance of catalyst **1** (53% and 61% yields, entries 2 and 3, Table 1). Higher yields (70% and 76%) of amine **4b**[12] along with traces of regioisomers[13] were obtained from coupling to the electron-deficient *p*-methoxycarbonylphenyl boronic acid, reflecting minimal boronic acid dimerization[14] (entries 8 and 9, Table 1). Ethyl *N*-aryliminoacetates bearing electron-withdrawing substituents Y (CF$_3$, COOMe) performed poorly ($<$15%) using catalysts **1** and **3**. Unexpectedly, Pd(OAc)$_2$ catalyst **3** proved to be notably more effective in coupling to the synthetically important *N*-PMP-protected[15] imines, providing amines **4c** and **4d** in better yields (54% and 74%, entries 12 and 13, Table 1) than the yields achieved with catalyst **1** (36% and 62%, entries 10 and 11, Table 1).[12] Traces of regioisomers were only detected in the crude products from entries 10 and 13 (Table 1).[13] The diastereocontrol[12] of coupling to *N*-PMP-protected imines (dr $>$ 10:1) is notable. The observed difference in selectivities of catalysts **1** and **3** might reflect the involvement of two distinct catalytic intermediates, complex **A** formed from catalyst **1** (Figure 1)[16] and complex **C** formed from catalyst **3** (Figure 2),[17] or a change in the rate-determining step. Amine **4a** prepared by a reaction catalyzed by complex **1** was essentially racemic, and optimization of the asymmetric induction has not yet been pursued.[18]

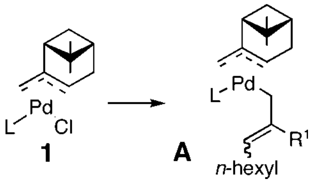


Figure 1. Catalytic intermediate arising from catalyst **1**.

A plausible catalytic cycle for the reactions catalyzed by Pd(OAc)$_2$ catalyst **3** is shown in Figure 2. Transmetalation[19] and migratory insertion[20] would provide intermediate **B** from catalyst **3**. Transmetalation to complex **B** would afford (aryl)(allyl)Pd(II)L complex **C**.[21] With the appropriate ligand L, complex **C**[21] would feature the allyl fragment in the η^1-bonding mode and undergo a nucleophilic allyl transfer

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(8) (a) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, B. *Chem. Commun.* **2002**, 1372. (b) Cleghorn, L. A. T.; Grigg, R.; Kilner, C.; MacLachlan, W. S.; Sridharan, V. *Chem. Commun.* **2005**, 3071.

(9) (a) Montgomery, J.; Song, M. *Tetrahedron* **2005**, *61*, 11440. (b) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (c) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076.

(10) (a) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304. (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.

(11) See additional results in the Supporting Information, including the details of the optimization studies and the importance of the auxiliary ligand choice, which affected the initial reaction rates without improvement in the yields of amines. A reaction catalyzed by Pd$_2$dba$_3$/HP(t-Bu)$_3$BF$_4$ under the same conditions afforded a 22% yield of amine **4a** (see the Supporting Information).

(12) Because amines **4a**−**d** are oils and the J(H2,H3) coupling constants in ^{1}H NMR spectra of the two diastereomers of amines **4a**−**d** have similar values, the relative stereochemistry could not be unequivocally assigned. See the Supporting Information.

(13) In entry 2, Table 1, traces ($<$3% of mass balance) of a mixture of several coupling products were present. The spectral pattern of this fraction was analogous to the byproduct fraction isolated from certain experiments described in Table 2, for which the structure assignment was realized. See ref 29.

(14) 4,4-Bis(methoxy)biphenyl was detected in the crude reaction mixtures (entries 2, 3, and 10, Table 1) by GC/MS. The observed decrease in the dimerization of the electron-deficient *p*-methoxycarbonylphenyl boronic acid agrees with known electronic effects. See: Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

(15) PMP = *p*-methoxyphenyl protecting group.

(16) For a catalytic cycle proposed by us for an analogous reaction mediated by catalyst **1**, see ref 6b.

(17) A symmetrical bis-π-allylpalladium complex featuring two “preassembled” allyl ligands (see ref 6b) appears to be an unlikely intermediate in the high-yielding reactions catalyzed by catalyst **3**, due to a complex pathway that would lead to its formation.

(18) The greater complexity of the allyl fragment in comparison to known cases (see ref 7) may cause the lack of facial selectivity in the allyl transfer from intermediate **A** (Figure 1).

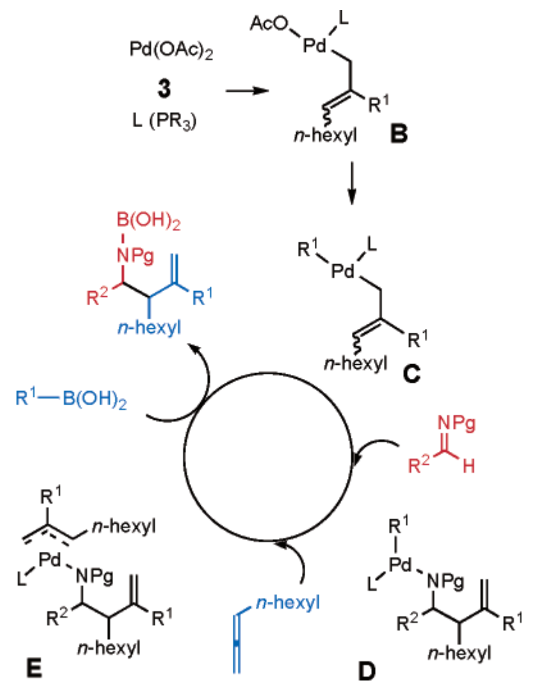
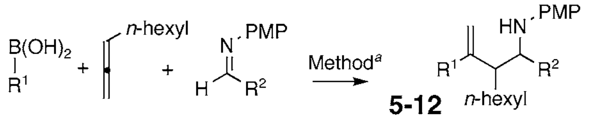


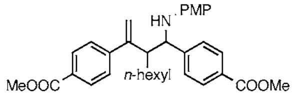
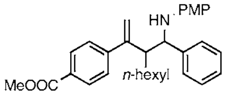
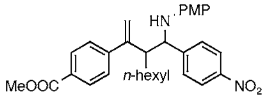
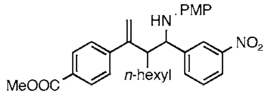
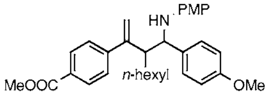
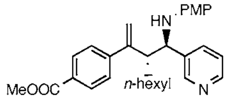
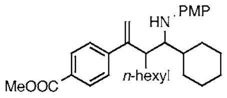
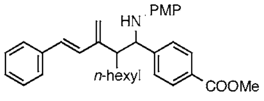
Figure 2. Proposed catalytic cycle for catalyst **3**.

to imines.[6,7,22] The allyl transfer[23] via either closed or open transition states[24] followed by an allene insertion into complex **D** would provide (allyl)(amido)Pd(II)L complex **E**, which would release the product and regenerate the catalytically active complexes upon transmetalation (Figure 2). The electronic effects in the *N*-aryl substituent are consistent with the involvement of the closed transition state.[25] The ligand effects[11] suggest the possibility of the transmetalation to intermediate **E** operating as the rate-determining step.[26]

Next, reactions with unactivated *N*-PMP-protected imines were explored (Table 2). Both the catalysts **1** and **3** were tested in coupling of *p*-methoxycarbonylphenyl boronic acid and 1,2-nonadiene with *N*-PMP-protected imines of *p*-methoxycarbonylphenyl- and phenylcarboxaldehydes, using the P(*t*-Bu)$_3$ ligand[27] (entries 1 and 2, Table 2). At room temperature, amines **5** and **6** were isolated in 40% (catalyst

Table 2. Three-Component Coupling to Unactivated Imines



entry	product		yield (%)^b	dr
1		**5**	67	50 : 1^c
2		**6**	61	50 : 1^c
3		**7**	62	50 : 1^c
4		**8**	62	50 : 1^c
5		**9**	47^d	8 : 1
6		**10**	57	50 : 1^c
7		**11**	64	50 : 1^c
8		**12**	68	7 : 1

^{a} Method: boronic acid/allene/imine = 2:5:1 (mol equiv), 10 mol % of Pd(OAc)$_2$, 10 mol % of HP(*t*-Bu$_3$)BF$_4$, CsF (4 equiv), THF, 40 °C, 24 h. ^{b} Isolated yields. ^{c} No traces of the minor diastereomer were detected by ^{1}H NMR. ^{d} Reaction run at rt.

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[19] CsF serves to activate the boronic acid for transmetalation, simultaneously releasing the phosphine ligand from its tetrafluoroborate salt. See: (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095. (b) Netherton, M. R.; Fu, G. *Org. Lett.* **2001**, *3*, 4295. For transition-metal-catalyzed reactions of boronic acids with dienes, aldehydes, imines, and enones, see: (c) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567. (d) Oh, C.-H.; Ahn, T.-W.; Reddy, V. R. *Chem. Commun.* **2003**, 2622. (e) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450.

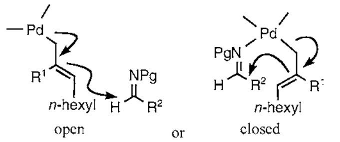
[20] For Pd-catalyzed reactions of allenes, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. For a review of the allene chemistry, see: (b) Krause, N.; Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004.

[21] For reactions of stoichiometric (allyl)(aryl)Pd(dppe) complexes with electrophiles, see: Kurosawa, H.; Urabe, A. *Chem. Lett.* **1985**, 1839.

[22] The η^1-bonding of the allyl ligand to the Pd-center via the unsubstituted carbon was shown by computations to be a prerequisite of the nucleophilic reactivity, and also rationalizes the preferential formation of branched allyl products, see: (a) Wallner, O. A.; Szabo, K. J. *Chem.−Eur. J.* **2003**, *9*, 4025. (b) Szabo, K. J. *Chem.−Eur. J.* **2000**, *6*, 4413.

[23] Allylation via "free" allylboron reagents appears unlikely in the present system. In situ formation of allylboron reagents via a reductive transmetalation with Et$_3$B (reduction failed with Ph$_3$B) is known. See: Kumura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795.

[24] The structures of the possible transition states are:



[25] The poor reactivity of the electron-deficient electrophilic ethyl *N*-aryliminoacetate suggests the involvement of a closed transition state requiring the attachment of the N-heteroatom to the Pd(II) center. See ref 5b.

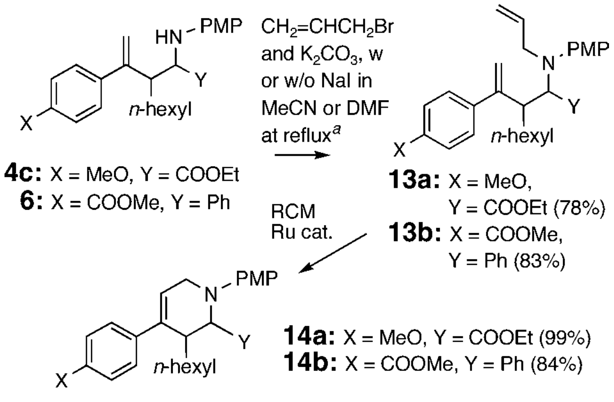
[26] To facilitate the *N*-Pd bond cleavage, the experiment reported in entry 3 (Table 1) was also run in the presence of 1.0 equiv of the Cu(OAc)$_2$ additive. See: Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. The reaction afforded amine **4a** in a slightly improved yield (64%).

[27] The choice of the auxiliary monodentate phosphine ligand was extensively optimized using GC/MS monitoring.

1) and 50% yields (catalyst **3**). At 40 °C, an improved 67% yield of amine **5** was achieved with both catalysts, whereas amine **6** was obtained in 54% (catalyst **1**) and 61% yields (catalyst **3**) (entries 1 and 2, Table 2).[28] In contrast to coupling with iminoacetates,[11] reactions with unactivated imines at room temperature afforded increased quantities (10−15% of the mass balance) of a fraction consisting of a mixture of regioisomers.[13] At elevated temperatures (40 °C), only traces of this fraction were produced (all entries in Table 2). The optimized protocol exploiting the $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyst at 40 °C was used to survey the coupling to *N*-PMP-protected aromatic, heteroaromatic, and aliphatic imines (entries 3−8, Table 2). With a single exception (entry 5), amines **7**, **8**, and **10**−**13** were isolated in good yields (57−68%) and with an excellent diastereocontrol (entries 1−4, 6, and 7, Table 2). The generation of a synthetically useful diene functionality in amine **12** is notable (entry 8, Table 2). The *p*-methoxyphenyl imine provided a better yield of amine **9** at room temperature (48% yield, entry 5, Table 2), giving rise to 18% mass of the byproduct fraction.[13,29] The components of this mixture were identified as two regioisomeric ketones and a branched alcohol,[29] likely arising via *β*-hydride elimination from regioisomeric amidopalladium complexes followed by imine hydrolysis or via a coupling to an aldehyde formed via hydrolysis of the imine substrate.[30] The anti relative stereochemistry of amine **10** (entry 6, Table 2) was revealed by single-crystal X-ray crystallographic analysis.[31]

The major diastereomers of ester **4c** and amine **6** were converted into tetrahydropyridines **14a**,**b**[32] via N-allylation followed by ring-closing metathesis[33] of amines **13a**,**b** (Scheme 2). The protocol demonstrates a simple pathway for the conversion of the amines **4**−**12** to medicinally relevant heterocycles.[1,4]

Scheme 2. Synthesis of Tetrahydropyridines[a]



[a] Amine **13a**: K_2CO_3, NaI, allyl bromide, MeCN, 80 °C, 23 h. Amine **13b**: K_2CO_3, allyl bromide, DMF, 120 °C, 9 h.

In conclusion, a new convergent and modular method for a regio- and diastereoselective preparation of branched homoallylic amines under mild conditions was described, exploiting a commercial Pd(II) catalyst.[6] Two new stereocenters and two carbon−carbon bonds are formed in one operation, providing products suited for elaboration to medicinally relevant heterocycles. The ability of the $Pd(OAc)_2$-derived catalytic system to catalyze effectively both the assembly of the allylpalladium intermediate and its umpolung allowing for the nucleophilic allyl transfer to imines is notable and remains unprecedented.

Acknowledgment. Acknowledgment is made to the Petroleum Research Fund of the ACS (41232-AC1) and to the Office of Science of the U.S. Department of Energy (DE-FG02-06ER15792) for support of this research.

Supporting Information Available: Description of the synthesis and characterizaton of all new compounds, optimization of the synthesis of amines **4**, and X-ray data on amine **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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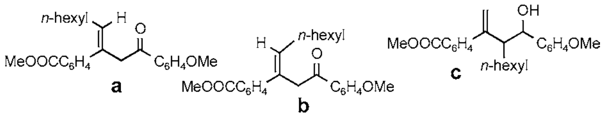
(28) Preparation of amine **5** at higher temperatures (67 °C) led to a lower yield (32%).

(29) Ketones **a** and **b** and alcohol **c** were present in the ratio **a**/**b**/**c** = 1.4:1.6:1 mol, e.g., 6.3%:7.2%:4.5%, on the basis of NMR analyses of partially separated mixtures from preparative TLC. See the Supporting Information.



(30) A control experiment involving three-component coupling to *p*-methoxyphenylcarboxaldehyde under the conditions of the experiment in entry 5 (Table 2) afforded a low yield (7%) of the mixture of compounds **a**, **b**, and **c**. See ref 29.

(31) The anti relative stereochemistry for amines **5**−**12** can only be assigned tentatively by analogy. The anti stereochemistry supports the operation of a closed transition state (see refs 24 and 25).

(32) Inconclusive NOE analyses and the failure to generate single crystals of amines **14** precluded the assignment of stereochemistry.

(33) (a) Chacun-Lefevre, L.; Beneteau, V.; Joseph, B.; Merour, J.-Y. *Tetrahedron* **2002**, *58*, 10181. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem.*−*Eur. J.* **2002**, *8*, 2034. (c) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.* **2005**, 1969.