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Domino Formation of Enamines - Intramolecular Cyclizations to 1-Aminotetralins from γ-Arylallene Aldehydes and Amines

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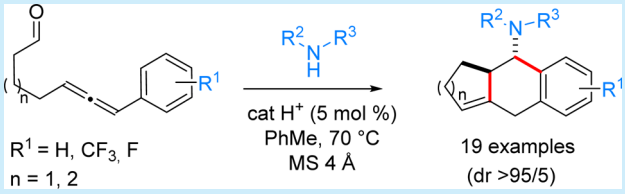
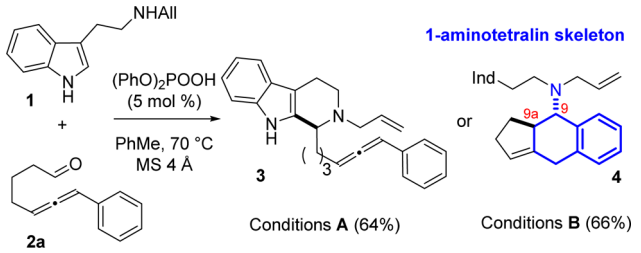
Supporting Information

ABSTRACT: 1,5-/1,6-Allenals conjugated to an aromatic ring undergo a cyclization, in the presence of an amine, that leads to tricyclic compounds including the 1-aminotetralin scaffold. This domino process combines the *in situ* formation of the enamine and the cyclization affording the tricyclic 1-aminotetralins in very high diastereoselectivities.



Nitrogen-containing compounds are of considerable importance for the pharmaceutical industry, and the search for novel scaffolds and novel, efficient synthetic routes constitutes a challenge for organic chemists.[1] Domino reactions[2] are powerful tools to gain efficiency, by reducing the number of steps and waste and by rapidly accessing molecular diversity in an atom economic[3] manner. This strategy was used successfully in the synthesis of heterocyclic compounds[4] and in total synthesis.[5] Following this approach we recently described the synthesis of indolo[2,3-*a*]-quinolizidines via a domino deprotection/cyclization strategy.[6] The Pictet–Spengler reactions catalyzed by phosphoric acids[7] between the *N*-allyltryptamine and hepta-5,6-dienals were used for the construction of tetrahydro- β-carbolines prior to cyclization. In this context, the reaction between *N*-allyltryptamine **1** and 7-phenylhepta-5,6-dienal **2a** under classical Pictet–Spengler conditions (Scheme 1, Conditions A) led to the tetrahydro-β-carboline **3** as the main product in 64% yield and with a moderate amount of an unknown compound, further identified as **4** (Scheme 1). Unexpectedly, when the stoichiometry of **1** and **2a** was modified to conditions B and were applied, the tricyclic compound **4** was obtained as the sole product in 66% yield and with total diastereocontrol in favor of the diastereoisomer presenting an *anti*-relationship between the substituents of carbons C9 and C9a (characterized by a coupling constant J_{H9-H9a} = 9.5 Hz). This novel compound **4** features the 1-aminotetralin skeleton with an additional cycle which, upon chemical transformation of the double bond, may potentially be further functionalized. The leading member of the 1-aminotetralin family is (+)-sertraline[8] (and its congeners tametraline or lometraline), a popular antidepressant (Zoloft). Common synthetic routes to 1-aminotetralins include Friedel–Crafts acylations followed by reductive amination,[9] Diels–Alder reactions,[10] or addition of a lithium anion to an imine.[11] Recently, more direct routes have been reported by Sutherland, via an elegant multibond forming domino strategy[12] and Masson, via a chiral phosphoric acid catalyzed cyclization between anilines and phenylacetaldehydes.[13]

Scheme 1. Unexpected Cyclization to 1-Aminotetralins[a]



[a]Conditions **A**: **1** (1 equiv)/ **2a** (3 equiv). Conditions **B**: **1** (2 equiv)/ **2a** (1 equiv).

In this paper, we report our investigations toward the diastereoselective synthesis of this novel family of tricyclic1-aminotetralins via a domino enamine formation/cyclization strategy from allenaldehydes **2**.

The conditions for the domino process were first examined. Initial conditions B were applied to 7-phenylhepta-5,6-dienal **2a** and diallylamine (2 equiv), used as a secondary amine devoid of an indolic core to avoid the competing Pictet–Spengler pathway. The corresponding tricyclic compound **5a** was obtained in 69% yield as a single diastereomer (Table 1, entry 1). The influence of the molecular sieves, the nature of the acid, the temperature, and the solvent were next studied. When the reaction was performed in the absence of either molecular sieves (Table 1, entry 1) or diphenylphosphate (Table 1, entry 2), the yield in **5a** dropped to 44% and 40%, respectively. Accordingly the role of the molecular sieves and the diphenyl phosphate seems to be not preponderant, but ensures a better yield in the final product. The nature of the acid was next investigated. The replacement of diphenyl phosphate by CF_3CO_2H or *p*-toluenesulfonic acid (PTSA) dropped the yields to 42% and 48%, respectively (Table 1,

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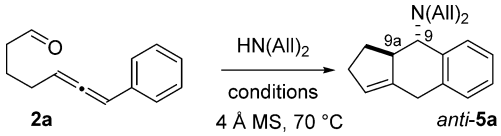
Table 1. Optimization of the Domino Reaction Sequence



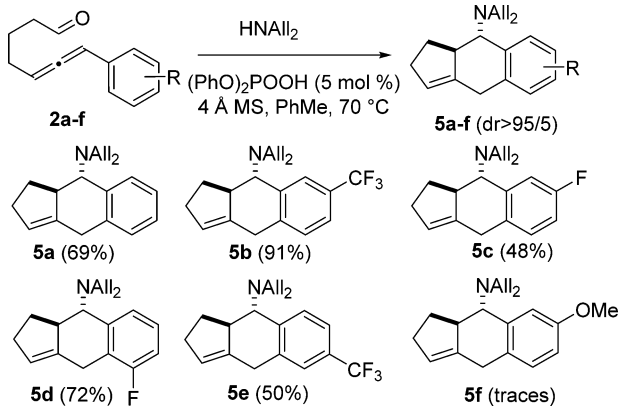
entry	solvent	acid source (5 mol %)	yield in **5a** (%)
1	PhMe	$(PhO)_2POOH$	69 (44)[a]
2	PhMe	–	40
3	PhMe	CF_3CO_2H	42
4	PhMe	PTSA	48
5	CH_2Cl_2	$(PhO)_2POOH$	35
6	THF	$(PhO)_2POOH$	47
7	DMF	$(PhO)_2POOH$	61

[a]Yield in parentheses was obtained without molecular sieves.

entries 3–4). Replacement of toluene by CH_2Cl_2, THF, or DMF also appeared detrimental to the yields (Table 1, entries 5–7). Initial conditions (5 mol % of diphenyl phosphate in the presence of molecular sieves in toluene at 70 °C) were selected for the following studies.

In order to demonstrate the broad applicability of our method, we prepared various allenals **2a–f**,[14] using the palladium-catalyzed Heck alkynylation of benzyl chlorides developed by Buchwald[15] and the Swern oxidation as key steps (see the Supporting Information). The reaction of aldehydes **2b–f** with diallylamine was studied under the conditions established above, in order to determine the influence of the R substituent on the aryl group on the outcome of the reaction (Scheme 2). In all cases, the expected

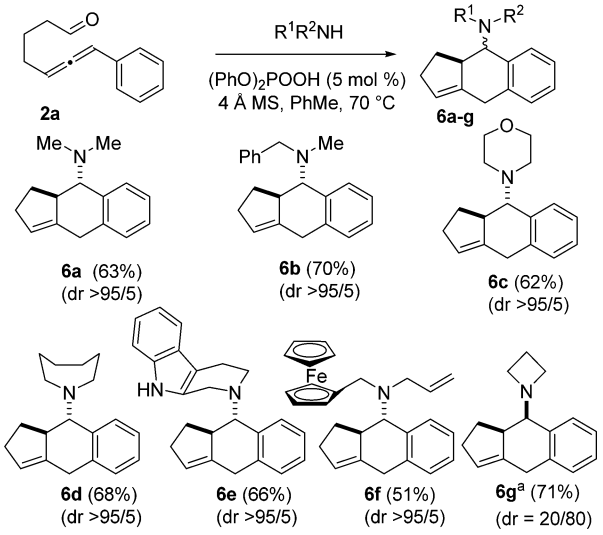
Scheme 2. Scope of the Reaction with Aldehydes 2a–f



products **5a–e** were obtained as single *anti* diastereomers in moderate to good yields. Interestingly, compound **5e** was obtained as a single regioisomer. The use of the *p*-OMe substituted electron-rich aldehyde **2f** furnished the cyclization product **5f** in only trace amounts.

The effect of the amine used in the reaction was then studied (Scheme 3). Tricyclic derivatives **6a–g** were obtained as diastereomerically pure compounds in most cases. Various secondary amines were used, and the reaction showed broad applicability. Acyclic amines such as dimethylamine or dissymmetric methyl benzylamine afforded the corresponding 1-aminotetralins **6a** and **6b** in good yields. Cyclic amines such as morpholine, azepine, and tetrahydro-*β*-carboline furnished the products **6c–e** in 62–68% yields. The ferrocenylmethyl allylamine led to the corresponding compound **6f** in 51% yield.

Scheme 3. Scope of the Amine on Aldehyde 2a



[a]Compound **6g** was obtained using modified conditions from azetidine hydrochloride and triethylamine. Under the same conditions compound **6d** was obtained in 45% yield and with full diastereoselectivity.

Incorporation of the biologically relevant azetidine ring[16] was then investigated. The use of azetidine hydrochloride and triethylamine furnished the tricyclic compound **6g** as a mixture of diastereomers (dr = 20/80) in favor of the *syn*-**6g**.[17] Under similar conditions, the reaction of aldehyde **2a**, azepine hydrochloride, and triethylamine afforded the product **6d** in a modest 45% yield, but as a single *anti* diastereomer, showing that the modification of the protocol is not responsible for the loss in diastereoselectivity. At present, we are unable to rationalize this difference in stereoselectivity using the azetidine as the amine component.

The method was extended to aldehydes **2g** and **2h**, possessing an additional CH_2 in the carbon chain compared to **2a–f**. The reaction of **2g** with azepine, methyl benzylamine, and morpholine afforded the corresponding hexahydroanthracenamine **7–9a** (Scheme 4). In comparison with the easy formation of compound **5** or **6**, the temperature of the reaction had to be increased to 110 °C in Schlenk tubes to ensure full conversion of the aldehyde **2g** in the tricyclic compounds **7–9a**. Compound **7a** was obtained in 67% yield whereas the products **8a** and **9a** were obtained in lower yields. Interestingly, when electron-deficient aldehyde **2h** was reacted with the same amines, the corresponding hexahydroanthracenamines **7–9b** were obtained in yields up to 70%. The tricyclic compounds **7–9** were exclusively obtained as *anti* diastereomers, as confirmed by X-ray diffraction studies on crystals of compound **9a**.

Mechanistically, the first step of the process is the *in situ* $(PhO)_2POOH$ catalyzed formation of the iminium (*i*) (Scheme 5), by reaction of the aldehyde **2** with the secondary amine, which undergoes tautomerization to the corresponding enamine (*ii*) ensuring the regeneration of the acid catalyst. The product may then be obtained by either a stepwise (Path 1) or concerted (Path 2) mechanism. In Path 1, the addition of the enamine (*ii*) on the central position of the allene leads to the reactive iminium (*iii*) that would undergo an aza-Friedel–Crafts addition to furnish **5**. It is unclear whether the acid catalyzes the cyclization by protonation of the allene. Our efforts directed to the isolation of the pure enamine (*ii*) in

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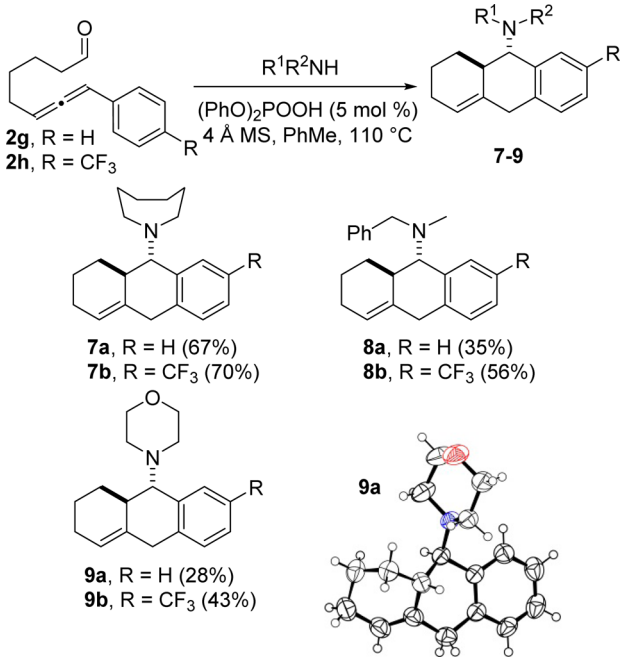
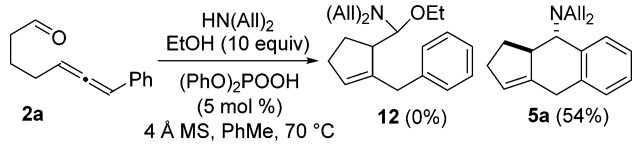
Scheme 4. Synthesis of Hexahydroanthracenamines 7−9 and Ortep Drawing for Compound 9a



Scheme 6. Iminium Trapping Attempt



order to study the cyclization process failed, giving in all cases the product **5**. Intermediates **10**−**11** (Scheme 5) described by Dake[18] as well as Zhu and Masson[19] are known to undergo Friedel−Crafts addition, favored by electron-rich aromatics. Conversely, the reaction reported in this paper is favored by electron-withdrawing groups (Scheme 2), which should facilitate the addition of the enamine on the allene (*ii*) by enhancing its electrophilicity, but strongly disfavor the Friedel−Crafts addition of the aromatic on the iminium (*iii*).[20] In addition, Masson and Zhu successfully trapped intermediate **11** by EtOH to interrupt the reaction,[19] thereby establishing the stepwise mechanism of the phosphoric acid catalyzed Povarov reaction.[21] In our hands, the reaction of aldehyde **2a** and diallylamine performed in the presence of 10 equiv of EtOH (Scheme 6) only led to classical compound **5a** in 54% yield, with no evidence for the formation of hemiaminal **12**. These last observations, along with the excellent diastereoselectivity of the reported reaction,[22] do not support the stepwise mechanism.

The second pathway (Path 2, Scheme 5) is similar to an intramolecular Diels−Alder reaction[23] with inverse electron demand from an *E*-configured enamine, followed by a rearomatization step of (*iv*). In this scenario the 1-aryl-1,2-propadienyl part acts as the diene, which undergoes substitution by electron-withdrawing groups, increasing the reactivity, as expected. While the use of electron-rich enamines as dienophiles[24] and of vinyl-aryls (styrenes) as dienes is known,[25] the allenyl-aryl moiety is not known for this type of reactivity yet.[26] The excellent *anti*-diastereoselectivities obtained in most cases are also in good agreement with the exquisite *anti*-diastereocontrol resulting from Diels−Alder cycloadditions of *trans* dienophiles. We therefore consider this pathway as the most probable.

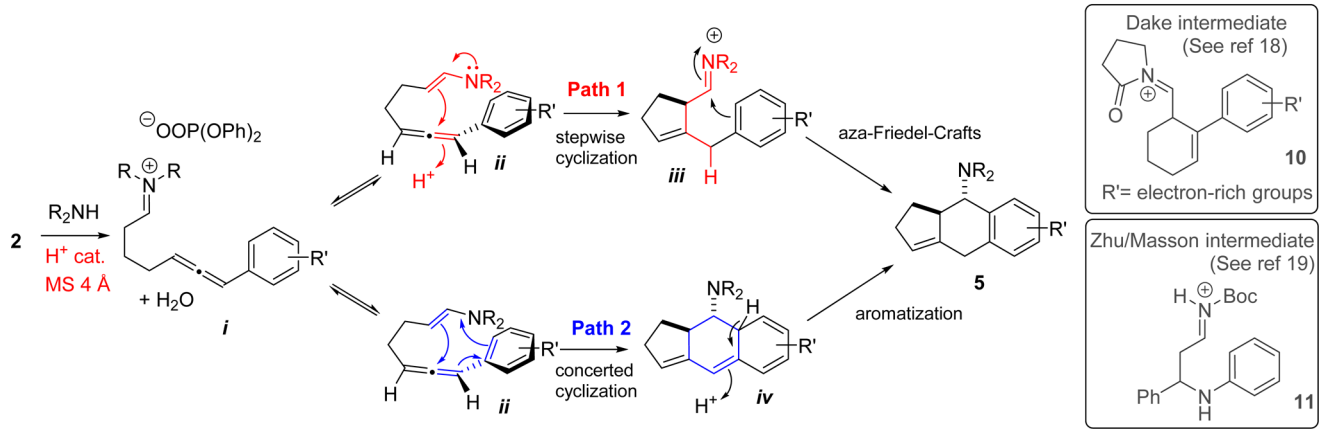
In conclusion, we have described the synthesis of various allenals **2** bearing aryl groups in the γ-position and studied their reactivity with secondary amines. We found that these reactions lead to potentially biologically relevant tricyclic 1-amino-tetralins **5**−**6** and their 6,6,6-tricyclic congeners **7**−**9** with high diastereoselectivities, via a process creating three bonds and two stereogenic centers. The reaction is favored by electron-withdrawing groups on the aryl. The mechanism of this novel transformation features a domino process with the *in situ* formation of the enamine followed by cyclization. It is not certain yet whether the cyclization proceeds via a stepwise or a concerted mechanism, but experimental data tend to favor the concerted one. Further studies are ongoing to gain better insight into this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 5. Mechanistic Hypotheses



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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Naito, T. *Chem. Pharm. Bull.* **2008**, *56*, 1367. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

(3) Trost, B. M. *Science* **1991**, *254*, 1471.

(4) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341.

(5) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(6) Gobé, V.; Guinchard, X. *Org. Lett.* **2014**, *16*, 1924.

(7) (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (c) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. (d) Huang, D.; Xu, F.; Lin, X.; Wang, Y. *Chem.—Eur. J.* **2012**, *18*, 3148.

(8) (a) Sarges, R. *J. Org. Chem.* **1975**, *40*, 1216. (b) Sarges, R.; Constantine, J. W.; McShane, W. K. *J. Pharm. Exp. Ther.* **1975**, *192*, 351. (c) Sarges, R.; Koe, B. K.; Weissman, A.; Schaefer, J. P. *J. Pharm. Exp. Ther.* **1974**, *191*, 393. (d) Sarges, R.; Tretter, J. R.; Tenen, S. S.; Weissman, A. *J. Med. Chem.* **1973**, *16*, 1003. (e) Fisher, M. J.; Backer, R. T.; Husain, S.; Hsiung, H. M.; Mullaney, J. T.; O'Brian, T. P.; Ornstein, P. L.; Rothhaar, R. R.; Zgombick, J. M.; Briner, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4459.

(9) (a) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879. (b) Han, Z.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5345. (c) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (d) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239.

(10) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028.

(11) Chen, C. y.; Reamer, R. A. *Org. Lett.* **1999**, *1*, 293.

(12) Grafton, M. W.; Farrugia, L. J.; Sutherland, A. *J. Org. Chem.* **2013**, *78*, 7199.

(13) Dagousset, G.; Erb, W.; Zhu, J.; Masson, G. *Org. Lett.* **2014**, *16*, 2554.

(14) (a) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (b) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259. (c) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

(15) (a) Larsen, C. H.; Anderson, K. W.; Tundel, R. E.; Buchwald, S. L. *Synlett* **2006**, *2006*, 2941. (b) Alternatively we also used the methods derived from the Crabbe reaction: Searles, S.; Li, Y.; Nassim, B.; Lopes, M. T. R.; Tran, P. T.; Crabbe, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747. (c) Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49*, 7230. (d) Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763. (e) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786.

(16) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

(17) The *syn* diastereomer presents a well-defined doublet at 3.18 ppm for H9 with a coupling constant of $J_{H9\text{-}H9a}$ = 3.3 Hz, characteristic of a *gauche* relationship with adjacent proton H9a; the *anti* diastereomers of the series show for H9 doublets with $J_{H9\text{-}H9a}$ ranging from 9 to 10 Hz.

(18) (a) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367. (b) Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929. (c) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585. (d) Dake, G. R. *Synlett* **2012**, 814.

(19) (a) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546. (b) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804.

(20) Conversely, this step should be favored by OMe groups, which leads to no product.

(21) (a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (b) Bello, D.; Ramón, R.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332. (c) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902. (d) Fochi, M.; Caruana, L.; Bernardi, L. *Synthesis* **2014**, *46*, 135.

(22) Intermediates **10** described by Dake undergo Freidel–Crafts addition with moderate to excellent diastereoselectivities.

(23) (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779.

(24) Zhang, J.; Taylor, C.; Bowman, E.; Savage-Low, L.; Lodewyk, M. W.; Hanne, L.; Wu, G. *Tetrahedron Lett.* **2013**, *54*, 6298.

(25) (a) Carreño, M. C.; Mahugo, J.; Urbano, A. *Tetrahedron Lett.* **1997**, *38*, 3047. (b) Kolis, S. P.; Chordia, M. D.; Liu, R.; Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2218. (c) Pedrosa, R.; Andrés, C.; Nieto, J. *J. Org. Chem.* **2002**, *67*, 782. (d) Fadel, F.; Titouani, S. L.; Soufiaoui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905.

(26) (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (d) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (e) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91. (f) Ma, S. M. *Chem. Rev.* **2005**, *105*, 2829. (g) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.