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# Improvements of the total synthesis of monocillin I and radicicol via Miyaura–Suzuki couplings

Isabelle Tichkowsky and Robert Lett*

*Unité Mixte CNRS-AVENTIS Pharma (UMR 26), 102, route de Noisy, 93235 Romainville, France*

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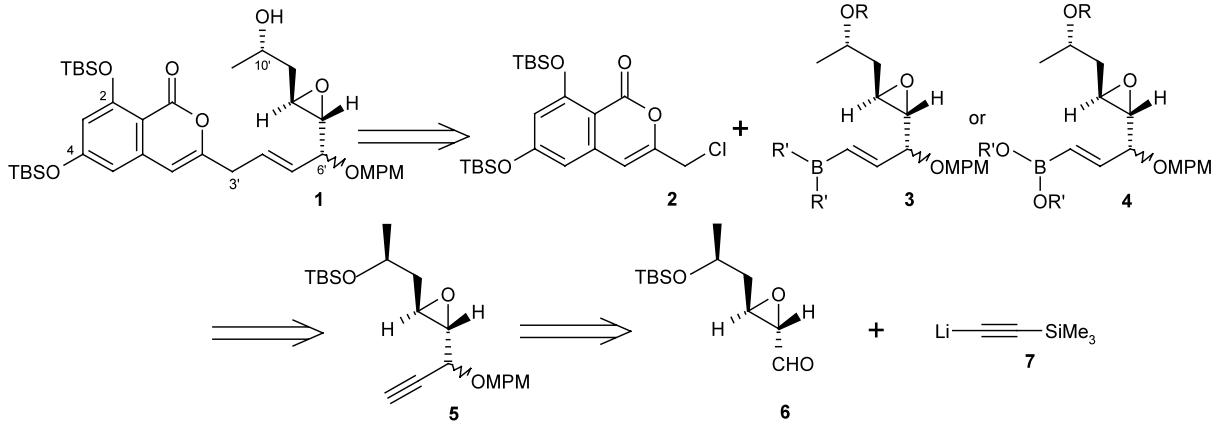
**Abstract**—The palladium-catalyzed coupling of the vinyldisiamylborane, formed in situ, affords the isocoumarins which can be used further for the synthesis of radicicol and related macrolides, in 72% global overall yield from the alkyne. Advantages over related vinylboronates or vinyltin couplings are discussed in the case of the present examples. 

The convergent approach we developed for the first total synthesis of monocillin I and radicicol involved the palladium-catalyzed coupling of a functionalized enantiopure vinylstannane and an appropriate chloromethylisocoumarin as a key-step.[1–3] Our scheme was quite flexible for studying related Miyaura–Suzuki couplings of vinyldialkylboranes **3** or vinyldialkylboronates **4**,[4] according to Scheme 1.

Boron a priori had the following advantages over tin chemistry: regio- and stereospecificity of the hydroboration of terminal alkynes, much cheaper reagents, much easier purification of the products and avoiding tin contaminants. However, it was necessary to be able to achieve the efficient hydroboration of the alkyne, in the presence of the epoxide and of the propargylic OMPM ether which should also diminish—by its inductive effect—the nucleophilic character of the triple bond; a situation which to our knowledge had no precedent. Moreover, it was particularly challenging to study Miyaura–Suzuki couplings here, since we were aware of the high sensitivity of the coupling product to mild basic conditions: when trying to find suitable conditions for the isocoumarin cleavage, even at rt, dilute NaOH (0.01 M) or dilute $NaHCO_3$ in $H_2O$/DME (1/1) immediately only induced degradation and the formation of numerous products due mostly to the highly activated methylene at the 3′ position.[1] On the other hand, there was no appreciable degradation in strictly anhydrous conditions with $K_2CO_3$ in THF or DME (reflux).




**Scheme 1.**

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* Corresponding author. Tel.: 33-1 49 91 52 80; fax: 33-1 49 91 38 00; e-mail: robert.lett@aventis.com

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Therefore, in the case of the coupling of halides with vinylic boron derivatives, the conditions developed just before we began this work by Suzuki and co-workers, using $K_2CO_3$ or $K_3PO_4$ as a base in THF or dioxane[5] instead of NaOH or NaOR (R = Me, Et) which were almost generally employed before, appeared to us to be more promising for preserving the structure of the coupling product. Since a base is required for the Suzuki couplings[4] and we checked that in the present examples,[2] an other important problem was to keep the phenol OTBS protective groups, especially the *para* 4-OTBS which was optimal for the further completion of the synthesis.[1]

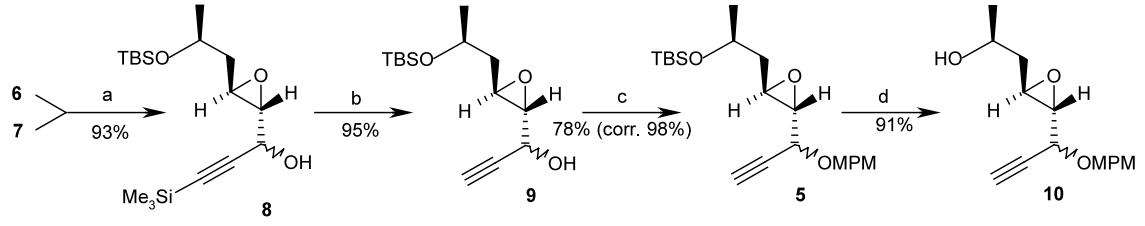
The required alkynes **5** and **10** were prepared from the same enantiopure epoxyaldehyde **6** we used in our first approach[1] (Scheme 2). The condensation of **6** and **7**, in THF/hexane (3/2) (−35°C to 0°C) afforded the two diastereoisomers, epimeric at 6′, in 93% yield (in a ratio 2/1); the reaction of **7** in the presence of $CeCl_3$ (1 equiv.) was not stereoselective (89% yield, 1/1 ratio). As we showed in the preceding communication, quite fortunately the two adducts can be used for the synthesis of monocillin I and radicicol.[3] Consequently, the whole work described herein was achieved starting with the 2/1 mixture of adducts **8** and careful examination of the isolated synthetic intermediates showed there was no significant variation of this ratio throughout the whole sequence. Model studies on simpler acetylenic epoxides showed that catecholborane led to competitive epoxide opening and that either dicyclohexylborane or disiamylborane (generated in situ in THF from the olefin—freshly redistilled over $CaH_2$—and the $BH_3{\cdot}Me_2S$ complex ≠10 M) were quite efficient for achieving the regio- and stereospecific hydroboration of the terminal alkyne with no epoxide opening. Hence, after preliminary optimization, one-pot couplings could be achieved in quasi-stoichiometric conditions, affording the coupling product in quite comparable yields, either with vinyldicyclohexylboranes or the derived boronates (after in situ oxidation by $Me_3NO$). The best solvents were found to be benzene, DME, 1,4-dioxane or AcOEt in a 90/10 mixture with $H_2O$.[2]

Influence of the nature of the palladium catalyst was studied for optimizing the coupling of the vinyl-dicyclohexylboronate, generated in situ from the alkyne **5**, with the bromomethylisocoumarin **11** and some results obtained in the conditions specified in Scheme 3 are given in Table 1.

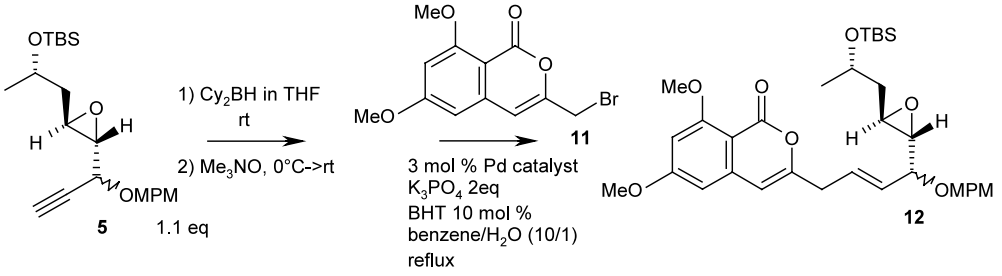
For the same one-pot coupling of the vinyldicyclohexylboronate, using 1.5 mol% $Pd_2(dba)_3$ as the source of palladium and in the presence of 4 equiv. of phosphine/Pd, yields of the coupling product obtained in the presence of BHT (or not) are given in Table 2. Concerning the ligand,[6] the whole data show that in this case there is no direct correlation between the steric or electronic effects and the efficiency of the coupling. Ligands as different as $PPh_3$, P(*o*-tolyl)$_3$, (3-$MeOC_6H_4)_3P$, $AsPh_3$, and dppf here give quite com-

**Table 1.** Pd catalytic system (3 mol%) and yield of **12** (Scheme 3)

| | |
|---|---|
| $Pd(PPh_3)_4$ | 55–75% |
| $PdCl_2(PPh_3)_2 + 2DIBAH$ | 48% |
| $Pd(OAc)_2 + 2PPh_3$ | 57% |
| $Pd(OAc)_2 + 4PPh_3$ | 56% |
| $PdCl_2(CH_3CN)_2 + 2PPh_3$ | 62% |
| $PdCl_2(PPh_3)_2$ | 62% |
| $1/2Pd(dba)_3 + 4PPh_3$ | 46% |
| $PdCl_2$dppf | 56% |
| $[PhPd(\mu OH)(PPh_3)_2]$ | 56% |




**Scheme 2.** *Reagents and conditions*: (a) **7** (1.5 equiv.) from trimethylsilylacetylene (2.0 equiv.) and *n*-BuLi (1.5 equiv.) in THF/hexane (2/1), −60°C, then addition of **6** in THF at −35°C, THF/hexane (3/2), 2 h at −35°C and 12 h at 0°C; (b) $K_2CO_3$ (1 equiv.), MeOH, rt, 30 min; (c) BuLi (1 equiv.)/THF/hexane (1/1), −78°C, then MPMCl (1.5 equiv.), HMPA, 48 h, rt; (d) TBAF 1 M in THF (1.1 equiv.), rt, overnight.




**Scheme 3.**

**Table 2.** Influence of the ligand, with 10 mol% BHT or without BHT, on the yield of **12** with 3 mol% Pd catalyst (Scheme 3)

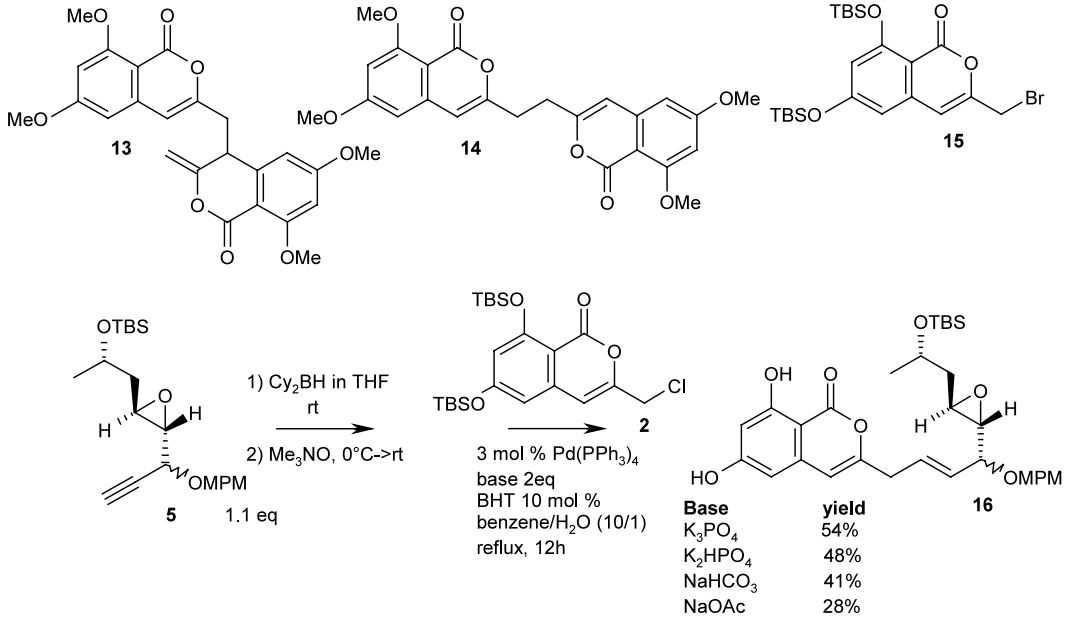
| Ligand | Yield (no BHT) | Yield (10% BHT) | Time |
|---|---|---|---|
| $PhMe_2P$ | 13% | | 12 h |
| $Ph_2MeP$ | Trace | | 12 h |
| $Ph_3P$ | | 46% | 60–90 min |
| $(4\text{-}ClC_6H_4)_3P$ | | 40% | 50 min |
| $(4\text{-}MeOC_6H_4)_3P$ | | 33% | 30 min |
| $(4\text{-}Me_2NC_6H_4)_3P$ | | 35% | 1 h |
| $(3\text{-}ClC_6H_4)_3P$ | | 35% | 1 h |
| $(3\text{-}MeOC_6H_4)_3P$ | | 44% | 1 h |
| $(2,4,6\text{-}(MeO)_3C_6H_2)_3P$ | 35% | 36% | 5–10 min |
| $(2\text{-}MeC_6H_4)_3P$ | 50% | 51% | 2 h |
| $Ph_2PCH_2CH_2PPh_2$ | 18% | | 12 h |
| $(2\text{-Furyl})_3P$ | | 31% | 12 h |
| $(3\text{-}SO_3C_6H_4)_3PNa_3$[a] | | 25% | 12 h |
| $(PhO)_3P$ | | 31% | 12 h |
| $Ph_3As$ | 36% | 50% | 15 min |

[a] In this case benzene/$H_2O$ 75/25.

parable yields, showing that there is no real rate determining step in the catalytic cycle, that is no great energy differences between the catalytic species involved in the different steps. Addition of CuI (1 equiv.)[7] in the presence of 3 mol% $Pd(PPh_3)_4$, keeping otherwise the same conditions as in Scheme 3, led to a faster coupling, but to unstable catalytic species, thus affording **12** in 15% yield after 2 h with other by-products.

Quite comparable yields of coupling product were obtained with either the bromomethylisocoumarin **11** or the chloromethylisocoumarin **2**, as we already noticed for the couplings of the related vinylstannanes.[1–3] However, full deprotection of the TBS protective groups of the phenols occurred in the same conditions with the chloromethyl–isocoumarin **2**, and only **16** was produced; use of a weaker base also afforded only **16** (Scheme 4). No solution to this problem was found with the use of the bromomethylisocoumarin **15**.

The role of BHT[8] was shown to be quite complex and not only related to the eventual quench of radicals formed in the presence of traces of oxygen or due to the autoxidation of organoboranes: addition of BHT sometimes improved the coupling or had no effect; in fact, the coupling in the presence of other quenching agents of oxygenated radicals such as duroquinone or galvinoxyl (0.1 equiv.) occurred in lower yield than the same coupling with no BHT or even with no argon atmosphere (at solvent reflux); on the other hand, addition of 10 mol% *p*-dinitrobenzene or 1 equiv. nitrobenzene had no significant effect on the yield of the coupling.[2] We observed however that addition of BHT clearly diminished the formation of **13**,[2] **14** always being a minor by-product (less than 3%); compounds which were also isolated in some couplings of the analogous vinyl-tributylstannanes.[1a] Thus, for the coupling corresponding to Scheme 3 with $Pd_2(dba)_3$ and $AsPh_3$ (Table 2), **13** was isolated in 11% and 20–25% yield, respectively, in the presence of 10 mol% BHT and in the absence of BHT, when consistently **12** was obtained in 50% and 30–35% yield. On the other hand, in the case of the vinyl-dicyclohexylboronates generated in situ, the yield of the desired coupling product was sometimes limited in some reaction conditions by the competitive formation of **17**, resulting not from a radical coupling but from a palladium-catalyzed homocoupling of the vinylboron component,[9] as clearly shown by the high stereoselectivity of its formation since only the *E,E*-diene was formed ($^1H$ NMR at 400 MHz, and $^{13}C$); moreover we showed that **17** was formed in the same reaction conditions, in the absence of the isocoumarin, and that the formation of **17** was not diminished, but even significantly enhanced with 10 mol%

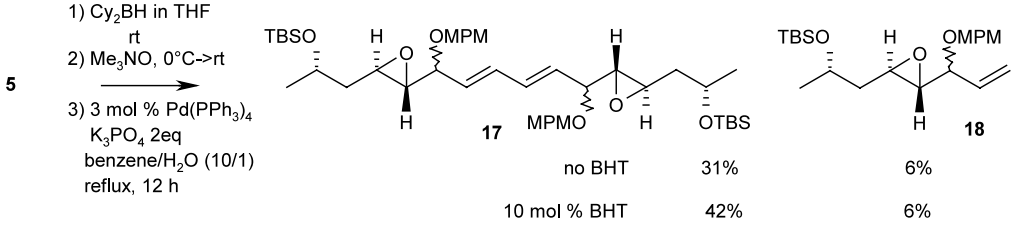



**Scheme 4.**

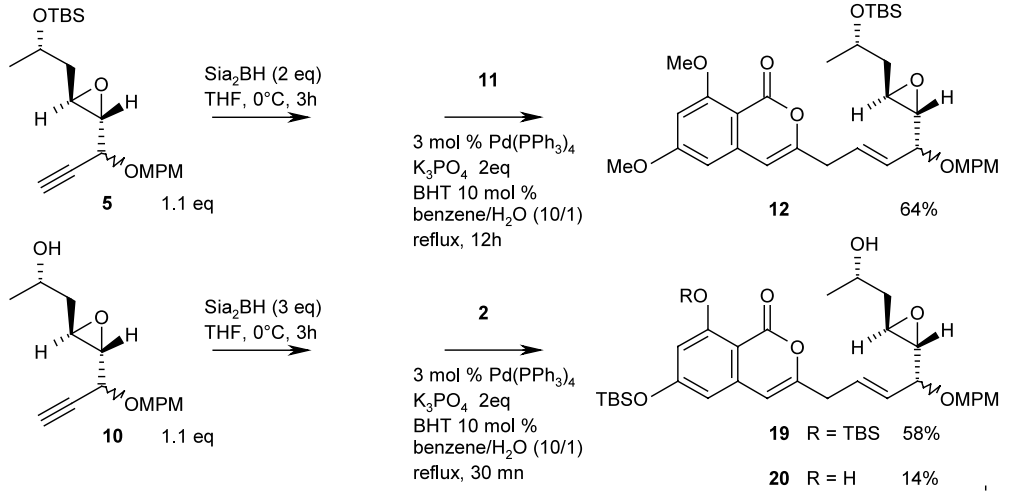
BHT (Scheme 5). These same experiments also showed that protonolysis in the reaction conditions was not important.

In order to try to diminish that homocoupling reaction, we decided to examine more hindered boranes for making the oxidative addition of Pd° more difficult than on the previous vinyldicyclohexylboronates. Taking also in account the results we obtained in preliminary studies on simpler models for related (10′-desoxy) vinyldicyclohexyl-boranes and -boronates (10′-desoxy),[2] we thus studied related couplings with vinyldisiamylboron derivatives. After some optimization, the couplings described in Scheme 6 could be achieved and, in those experiments, only traces of **17** were observed. Quite interestingly, the one-pot coupling could be successfully achieved on the deprotected alcohol with the vinyldisiamylborane generated in situ from **10**; this was fortunate since oxidation by $Me_3NO$ of the corresponding vinyldicyclohexylborane proved to be troublesome and the desired coupling product was then not obtained.[2] Therefore, we could avoid the difficult problem of the specific deprotection of the 10′-OTBS ether in the presence of the phenol OTBS ethers which would have been required otherwise for the completion of the synthesis, moreover for finding conditions preserving the structure of the coupling product. During our study, in the present examples, we observed that in fact the couplings of those vinyldisiamylboranes are also faster than those of the related vinyldicyclohexylboronates; thus, after 30 min in the conditions described in Scheme 6, we could isolate the desired isocoumarins **19** and **20** in, respectively, 58 and 14% yield (72% global yield), in which the *para*-phenol was still protected as a TBS ether; the mixture of **19** and **20** as such could be used further in the synthesis, since the next two-step sequence for the isocoumarin cleavage (DIBAH reduction, $NaClO_2$ oxidation) leads to a specific total deprotection of the *ortho*-phenol TBS ether and that this free phenol is required for favoring the macrolactonization in Mitsunobu reaction conditions.[1–3]

In conclusion, for the examples studied herein, we showed that vinyldisiamylboranes have the following advantages over the corresponding vinyldicyclohexylboranes or boronates: minimization of the formation of the diene **17** resulting from a palladium-catalyzed homocoupling and hence higher yields of the desired product in quasi-stoichiometric conditions, phenol TBS protective groups can be preserved, suppression of the oxidation step of the borane into the boronate by $Me_3NO$ (which moreover here allows to achieve the coupling with the vinyldisiamylborane derived from the free 10′-OH alkyne **10** in a high yield). Hence, the modification described herein affords the desired isocoumarins for further completion of the synthesis in 45% overall yield from the same epoxy-aldehyde **6**, instead of 33% overall yield via the sequence developed previously with tin chemistry[1–3] (uncorrected yields).




**Scheme 5.**




**Scheme 6.**

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## References

1. (a) Lampilas, M. Ph.D. Thesis, Paris VI University, 1991; (b) Lampilas, M.; Lett, R. *Tetrahedron Lett*. **1992**, *33*, 773–776; (c) Lampilas, M.; Lett, R. *Tetrahedron Lett*. **1992**, *33*, 777–780; (d) Lett, R.; Lampilas, M.; Tichkowsky, I. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer Verlag, 1993; Vol. 2, pp. 99–120.
2. Tichkowsky, I. Ph.D. Thesis, Paris VI University, 1996.
3. Tichkowsky, I.; Lett, R. *Tetrahedron Lett*. **2002**, *43*, 3997–4001.
4. Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483.
5. (a) Abe, S.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 2863–2865; (b) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett*. **1992**, 691–694.
6. Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585–9595.
7. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem*. **1994**, *59*, 5905–5911.
8. (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem*. **1990**, *55*, 5833–5847; (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem*. **1993**, *58*, 5434–5444.
9. Miyaura, N.; Suzuki, A. *Main Group Met. Chem*. **1987**, *10*, 295–300.