CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201103209

Synthesis of Tetrasubstituted Alkenes through a Palladium-Catalyzed Domino Carbopalladation/C–H-Activation Reaction

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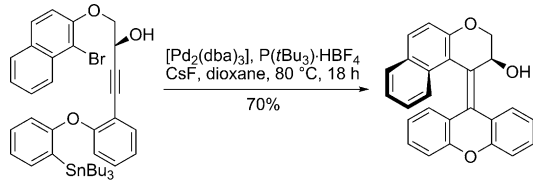
Abstract: Helical tetrasubstituted alkenes (**7**) were obtained in a highly efficient way through a palladium-catalyzed domino-carbopalladation/CH-activation reaction of propargylic alcohols **6** in good to excellent yields. Electron-withdrawing- and electron-donating substituents can be introduced onto the upper and lower aromatic rings. The substrates (**6**) for the domino process were synthesized by addition of the lithiated alkyne (**20**) to various aldehydes (**19**); moreover, the substrates were accessible enantioselectively (in 95% *ee*) by reduction of the corresponding ketone using the Noyori procedure.

Keywords: C–H activation · domino reactions · helical structures · molecular switches · palladium

Introduction

The development of ecologically and economically beneficial procedures for the synthesis of complex natural products and other interesting materials is one of the key issues in organic chemistry. In this respect, the concept of domino reactions, as introduced by ourselves, has become highly valuable, because it allows the synthesis of complex compounds in very few steps starting from simple substrates, it preserves our resources, and it reduces the amount of waste formed as well as the time needed.[1–3] Previously, we have prepared several natural products, such as α-tocopherol, using an enantioselective domino Wacker/Heck reaction.[4] We have also reported the preparation of enantio- and diastereomerically pure helical tetrasubstituted alkenes using a domino carbopalladation/Stille reaction.[5] Thus, the reaction of stannane **1** with $[Pd_2dba_3]$ (dba = dibenzylideneacetone) in the presence of $P(tBu)_3$ as a ligand gave compound **2** as a single enantiopure diastereomer (Scheme 1).

Though this procedure allowed the efficient and stereoselective access to tetrasubstituted alkenes of type **2**, the use of stannanes is neither environmentally friendly nor appropriate for a large-scale synthesis, because their preparation requires several additional steps. Thus, a cyclization through a C–H-activation pathway without introducing additional functional groups would be more beneficial.[6–12] For this purpose, we have investigated the palladium-catalyzed reaction of compound **4a** (Scheme 2).[13]



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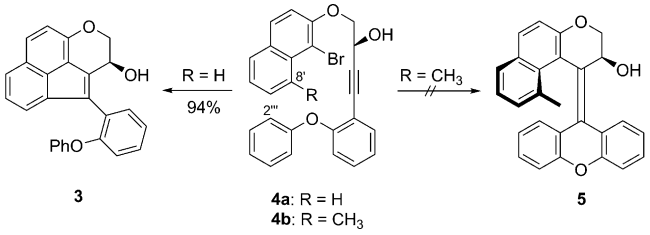
Scheme 1. Synthesis of tetrasubstituted alkene **2** from stannane **1**.



3 4a: R = H 4b: R = CH_3 5

Scheme 2. Formation of acenaphthylene **3** by a domino carbopalladation/C–H-activation reaction from alkyne **4**.

However, the only product that we obtained from this reaction was acenaphthylene **3**, which was formed from the carbopalladation of the triple bond, followed by a C–H activation at the C8′ position but not at the C2‴. All attempts to circumvent this reaction by, for example, introducing a methyl group at the C8' position (**4b**), did not lead to the formation of the desired tetrasubstituted alkenes of type **5**. However, by omitting the second aromatic ring in the naphthalene moiety in compound **4**, the synthesis of tetrasubsti-

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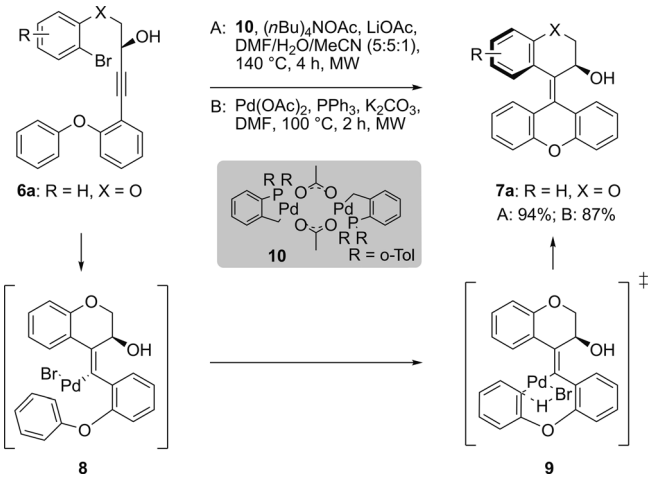
Supporting information for this article, including full syntheses and general procedures for all the of the synthesized compounds, is available on the WWW under http://dx.doi.org/10.1002/chem.201103209.

tuted alkenes via a domino carbopalladation/C–H-activation reaction could be accomplished with excellent results. Herein, we describe the synthesis of compounds of type **7** starting from compound **6** (Scheme 3).



Scheme 3. Domino carbopalladation/C–H-activation of compound **6a** to give compound **7a**.

Helical tetrasubstituted alkenes are of great interest as molecular switches and machines.[3,14] Thus, the development of new small devices for efficient electronic-data storage and processing has, in fact, been the focus of much research in materials science and, over the last few years, a multitude of publications have dealt with this area.[15–19]

Results and Discussion

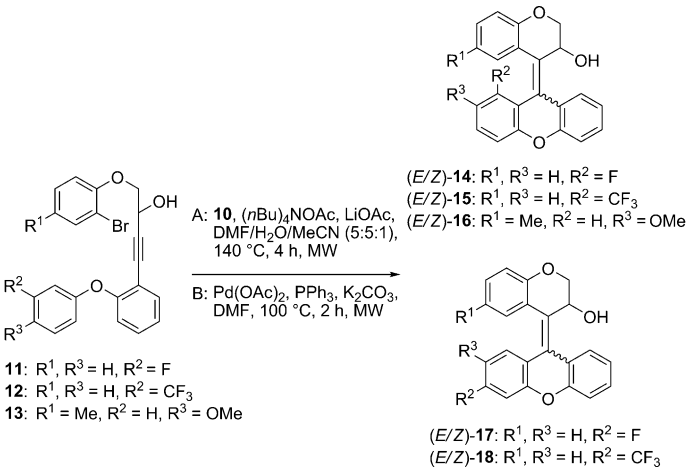
The reaction of compound **6a**, which contains a bromoarene moiety connected to an alkyne moiety, using the Hermann–Beller catalyst[20,21] (**10**) in the presence of tetrabutylammonium acetate and lithium acetate under microwave irradiation at 140 °C (method A) led to the formation of alkene **7a** in excellent yield (94 %), which is astounding, considering that no activating substituents (such as a triazoles, fluorine atoms, or trifluoromethyl groups) are present on the lower aromatic moiety. We assume that this excellent result is due to a proximity effect. Using palladium acetate in the presence of triphenylphosphine, again under microwave irradiation at 100 °C (method B), the yield was slightly lower but still very good (87 % yield). The scope of the reaction, in terms of substituents on the upper aromatic ring and exchanging the oxygen in the side chain for a CH_2 group, is quite broad, with both electron-donating and -accepting groups being successfully incorporated into the substituents, although varying yields were obtained from using the two different methods.[22] As can be seen from Table 1, method B usually gives better than—or almost identical yields to—method A, with the exception of substrate **7f**, where a high reaction temperature is presumably needed because of the steric demands of the *tert*-butyl groups.

Table 1. Synthesis of tetrasubstituted alkenes **7a–7k** from compounds **6a–6k**.

Entry	R (substrate)	X	Product	A[a,b] [%]	B[a,c] [%]
1	H (**6a**)	O	**7a**	94	87
2	4-Me (**6b**)	O	**7b**	59	57
3	4-F (**6c**)	O	**7c**	54	86
4	4-CF_3 (**6d**)	O	**7d**	72	91
5	4-CN (**6e**)	O	**7e**	49	41
6	4-*t*Bu (**6f**)	O	**7f**	74	38
7	4-OMe (**6g**)	O	**7g**	71	83
8	4,5-OCH_2O (**6h**)	O	**7h**	72	88
9	H (**6i**)	CH_2	**7i**	21	97
10	4-Me (**6j**)	CH_2	**7j**	44	60
11	4-CF_3 (**6k**)	CH_2	**7k**	54	75

[a] Yields of isolated products. [b] method A: LiOAc, $(nBu)_4NOAc$, Hermann–Beller catalyst **10**, DMF/MeCN/H_2O (5:5:1), 140 °C, 4 h, MW. [c] Method B: $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 100 °C, 2 h, MW.

Besides the introduction of a substituent onto the upper aromatic ring (**7a–7k**), compounds **11–13** (which are functionalized on the lower ring) can be successfully transformed to give tetrasubstituted alkenes (*E/Z*)-**14**–(*E/Z*)-**18** (Scheme 4). This study confirmed the activating effects of a



Scheme 4. Palladium-catalyzed transformations of compounds **11**, **12**, and **13**.

fluorine atom (**11**) or a CF_3-group (**12**) on the C–H-activation step in the domino process.[23] However, this reaction is more complicated than that of substrate **6**, because the C–H-activation can take place at the positions *ortho*/*para* to the fluorine atom in compound **11** or *ortho*/*para* to the CF_3-group in compound **12** to give compounds **14**/**15** and **17**/**18**, respectively, or mixtures of the two products. Furthermore, isomerization of the primarily formed *E* isomers to give the corresponding *Z* stereoisomers is expected. Finally, one has to assume that the steric hindrance of the products formed is much higher than that in compounds of type **7**.

As expected, the reaction of compound **11** using method A (140 °C) gave the four compounds, (*E/Z*)-**14** and (*E/Z*)-**17**, in 50 % yield as a 1:1 mixture of the *ortho*- and *para*-substituted products, and the reaction of compound **12** gave the four compounds, (*E,Z*)-**15** and (*E*/*Z*)-**18**, in 44 % yield as a 1:3 mixture in favor of the *para*-substituted products (*E*/*Z*)-**18**. These transformations show that there is an activation of the vicinal C–H bond through the F and CF_3 substituents, because products **14** and **15** are more-sterically hindered than compounds **17** and **18**. Furthermore, the CF_3 group has a higher steric demand than the F atom, thereby explaining the favored formation of the *para* product (**18**). Interestingly, the reaction of compound **12** using method B at 100 °C only led to the *para* product (**18**), again as an *E/Z* mixture (1:1) in 91 % yield, whereas the reaction of compound **13** afforded (*E*/*Z*)-**16** (1:1) in 94 % yield. The fluoro compound (**11**) gave only bad results under these conditions.

All of the precursors for the cyclization process contain a stereogenic center. Although most of the investigations were performed using racemic mixtures, the stereogenic center can easily be introduced in an enantioselective fashion. This fact was shown in an exemplary way for compound **6a** (see below), which, from a reaction with palladium acetate according to method B, gave compound (*S*)-**7a** in 83 % yield as a single, almost-enantiopure diastereomer.

In general, the tetrasubstituted alkenes **7a**–**7k** and compounds **14**–**18** are helical structures and can therefore exist in *P* and *M* forms, whereby during formation of the helix, the existing stereogenic center in the substrates completely controls the helicity in the products. Thus, (*S*)-**6a**–**6h** yields (*S,P*)-**7a**–(*S,P*)-**7h**, whereas (*R*)-**6i**–(*R*)-**6k** leads to (*R,P*)-**7i**–(*R,P*)-**7k**; for the enantiomers, the opposite induction is observed (taking into account the change in the priority of the substituents at the stereogenic center by exchanging the oxygen atom for a CH_2 group in the side-chain).[24]

The products are not configurationally stable but can isomerize. However, the calculations of the ground-state energies (Table 2) show that the *S,P* isomers (**7a** and **7d**) and the *R,P* isomers (**7i** and **7k**) are much-more-stable than the corresponding *S,M*- and *R,M* isomers, respectively. As an example, the difference in energy of the *P* form in comparison to the *M* form for (*R*)-**7k** is 26.4 kJ mol^{-1}. The X-ray data of (*rac*)-**7d** and (*rac*)-**7j** show that in the single crystal, compound **7d** exists as the *S,P*- and the *R,M* forms and compound **7i** as the *R,P*- and *S,M* forms (Figure 1).[25]

Table 2. DFT-calculations for ground state energies of the *P* and *M* form of selected tetrasubstituted alkenes of type **7**.[a]

Entry	Alkene	*P* form [kJ mol^{-1}]	*M* form [kJ mol^{-1}]	ΔE_{rel} [kJ mol^{-1}]
1	(*S*)-**7a**	−2818642.0	−2818621.8	20.2
2	(*S*)-**7d**	−3703793.6	−3703774.5	19.1
3	(*R*)-**7i**	−2724297.9	−2724273.2	24.7
4	(*R*)-**7k**	−3609451.5	−3609425.0	26.4

[a] Parameters of the DFT calculations: dataset B3LYP/6-311G(d,p) in MeCN as solvent.

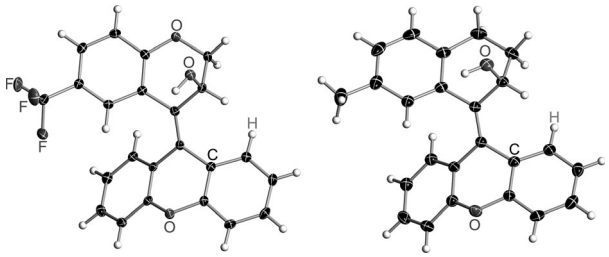
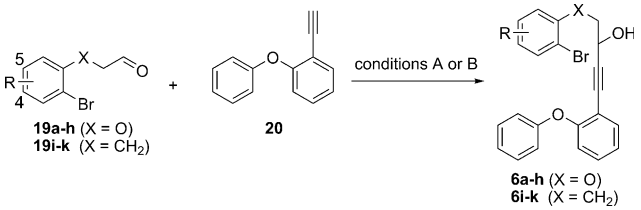
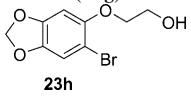


Figure 1. Molecular structures (ORTEP plots) of (*S,P*)-**7d** (left) and (*R,P*)-**7j** (right).

The synthesis of the substrates **6a**–**6k** for the domino process is straight forward; it is accomplished by the addition of the lithiated alkyne (**20**) to various aldehydes **19a**–**19k** (Table 3). However, the yields are not always reproducible and heavily depend on the both the quality of the metalating agent and on the speed of the addition of the aldehyde to the lithiated alkyne. In general, a syringe pump should be used to allow a slow and constant addition.

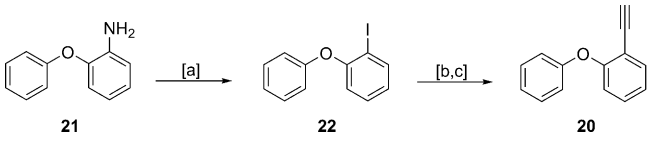
Table 3. Synthesis of propargylic alcohols **6a**–**6k** from the reaction of lithiated alkyne **20** with unpurified aldehydes **19a**–**19h**, obtained in situ from alcohols **23a**, **23d**–**23h**, acetals **23b** and **23c**, and purified aldehydes **19i**–**19k**.



Entry	R (substrate)	Conditions[a]	Product	X	Yield [%]
1	H (**23a**)	A	**6a**	O	56[b]
2	4-Me (**23b**)	A	**6b**	O	70[b]
3	4-F (**23c**)	B	**6c**	O	38[b]
4	4-CF_3 (**23d**)	A	**6d**	O	39[b]
5	4-CN (**23e**)	B	**6e**	O	40[b]
6	4-*t*Bu (**23f**)	A	**6f**	O	59[b]
7	4-OMe (**23g**)	B	**6g**	O	60[b]
8	 **23h**	B	**6h**	O	53[b]
9	H (**19i**)	A	**6i**	CH_2CH_2	64[c]
10	4-Me (**19j**)	B	**6j**	CH_2	62[c]
11	4-CF_3 (**19k**)	A	**6k**	CH_2	46[c]

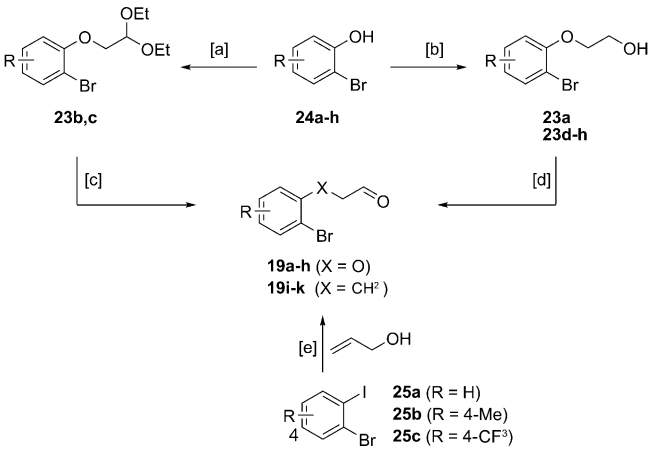
[a] Reaction conditions A: *n*BuLi, THF, −78 °C, then addition of aldehyde and stirring at −78 °C overnight; conditions B: LiHMDS, Et_3N, −78 °C, 15 min, −78 °C→RT, 1.5 h, then addition of aldehyde via syringe pump (1 mL h^{-1}) at −78 °C. [b] Yield of isolated products over two steps. [c] Yield of isolated products (1 step). LiHMDS = lithium bis(trimethylsilyl)amide.

The synthesis of alkyne **20** was accomplished by a Sandmeyer reaction of phenoxyaniline **21** to give compound **22**, followed by a Sonogashira reaction using ethynyltrimethylsilane (Scheme 5). The final step was the deprotection of the alkyne moiety; all steps proceeded with good yields.



Scheme 5. Synthesis of alkyne **20**. Reaction conditions: a) *p*TsOH, $NaNO_2$, KI, MeCN, RT, 2 h, 79%; b) ethynyltrimethylsilane, CuI, $[PdCl_2(PPh_3)_2]$, Et_3N, RT, 40 h, quant; c) K_2CO_3, $MeOH/CH_2Cl_2$(1:1), RT, 42 h, 94%.

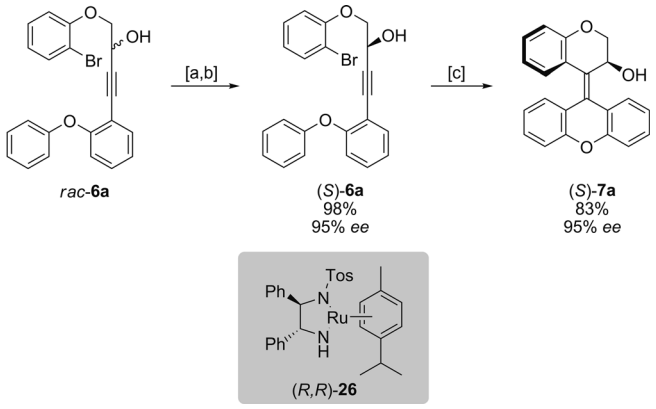
The aldehydes **19a**, and **19d–19h**, which contained oxygen-bridged tethers, were obtained by ether formation from the reaction of phenols **24a** and **24d–24h** with bromoethanol in the presence of potassium carbonate and catalytic amounts of crown ether 18-crown-6 to give alcohols **23a**, **23d–23h**, followed by oxidation of the hydroxy groups using IBX (Scheme 6). For the synthesis of aldehydes **19b**



Scheme 6. Synthesis of aldehydes **19a–19h** (with oxygen-bridged tethers) and **19i–19k** (with methylene-bridged tethers). Reaction conditions: a) bromoacetaldehyde dimethyl acetal, KOH, DMSO, 100°C, 21 h; b) K_2CO_3, [18]crown-6, MeCN, 4 Å molecular sieves, 60°C, 4–6 h, MW; [c] 10% HCl, THF, 40°C, 6–7 h; [d] IBX, MeCN, 4 Å molecular sieves, 40°C, 20 h; [e] allylic alcohol, $Pd(OAc)_2$, $(nBu)_4NCl$, $NaHCO_3$, DMF, 60°C, 6 h, MW. DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, MW = microwave, DMF = *N*,*N*-dimethylformamide.

and **19c**, acetals **23b** and **23c** were prepared by the reaction of phenols **24b** and **24c** using bromoacetaldehyde dimethyl acetal, followed by an acid-catalyzed cleavage of the acetal moiety. The aldehydes **19a–19h** are quite labile and purification by column chromatography on silica gel is not recommended. Thus, in all cases, they were used as unpurified compounds in the addition step with alkyne **20**. Aldehydes **19i–19k**, which contained a methylene group instead of an oxygen atom in the tether, were formed by an intermolecular Heck reaction of the bromoiodoarenes **25a–25c** with allyl alcohol (Scheme 6).[26] These aldehydes are stable and can be obtained in their pure form by column chromatography on silica gel in 71-85% yield.

For the enantioselective synthesis of compound **7a**, the racemic alcohol (*rac*)-**6a** was oxidized to give the corresponding propargylic ketone using Dess–Martin periodinane (Scheme 7). This oxidation was followed by transfer hydrogenation using isopropanol in the presence of the Noyori catalyst (*R*,*R*)-**26** to give compound (*S*)-**6a** in 98% yield and 95% *ee*.[27,28] Finally, as we have already mentioned, the diastereopure alkene (*S*)-**7a** was obtained in 83% yield and 95% *ee* from the domino reaction using palladium acetate in the presence of triphenylphosphine according to method **B**.[29]



Scheme 7. Enantioselective synthesis of alkene **7a**. Reaction conditions: a) DMP, CH_2Cl_2, RT, 25 h. [b] cat. (*R*,*R*)-**26**, *i*PrOH, MeCN, RT, 23 h. [c] $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 100°C, 2 h, MW. DMP = Dess–Martin periodinane.

Conclusion

The tetrasubstituted helical alkenes **7a–7k** were obtained in a highly efficient and diastereoselective manner through a palladium-catalyzed domino cabopalladation/C–H-activation using alkynes **6a–6k** as the substrates in good to excellent yields. A vinyl–aryl bond is formed by direct C–H activation, thereby avoiding the introduction of additional functional groups. This procedure also allows for the synthesis of almost-enantiopure compounds of type **7**, with the introduction of the stereogenic center in the substrate **6** by an enantioselective reduction of the corresponding ketone.

Experimental Section

Synthesis of 6i: General procedure for the alkynylation of aldehydes 19 (method A): A solution of alkyne **20** (663 mg, 3.42 mmol, 2.00 equiv) in dry THF (2.2 mL) was cooled to −78°C and then treated with *n*BuLi (2.5 M in hexanes, 1.40 mL, 3.42 mmol, 2.00 equiv). The reaction mixture was stirred for 30 min, before being allowed to warm to RT over 30 min and then was cooled again to −78°C. The cold solution was added slowly with stirring to a solution of aldehyde **19i** (365 mg, 1.71 mmol, 1.00 equiv) in dry THF (1.7 mL) at −78°C over 30 min using a syringe pump. After the addition had been completed, stirring was continued for 1.5 h; the mixture was allowed to warm to RT and the reaction was quenched by addition of saturated NH_4Cl (aq.) solution (30 mL). The mixture was extracted with *t*BuOMe (3×50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The

crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe, 5:1) to yield alcohol **6i** (445 mg, 64%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.76 (s, 1H), 1.89–2.01 (m, 2H), 2.84 (ddd, J=1.7, 6.9, 8.6 Hz, 2H), 4.49 (t, J=6.5 Hz, 1H), 6.93–6.98 (m, 3H), 7.01–7.06 (m, 2H), 7.08 (dt, J=1.1, 7.6 Hz, 1H), 7.16 (m, 2H), 7.26–7.31 (m, 3H), 7.48 (dd, J=1.7, 7.7 Hz, 1H), 7.50 ppm (d, J=7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=31.7, 37.3, 62.3, 81.1, 94.8, 115.2, 118.1 (2C), 119.6, 123.0, 123.6, 124.4, 127.4, 127.7, 129.6 (2C), 129.9, 130.6, 132.8, 133.7, 140.7, 157.4 ppm (2C); IR (ATR): $\tilde{\nu}$=2360 cm^{-1}, 1589, 1484, 1444, 1252, 1224, 1022, 750; UV/Vis (MeCN): λ_{max} (lg ε)=195 (4.881), 242 (4.229), 253 (4.200), 279 (2.453), 289 (3.489), 298 nm (3.405); MS (ESI, MeOH): m/z (%): 31.0 (24) $[M+Na]^+$, 837.1 (100) $[2M+Na]^+$; HRMS (ESI): m/z calcd for $C_{23}H_{19}BrO_2$: 429.0461 $[M+Na]^+$, 431.0441 $[M+Na]^+$; found: 429.0453, 431.0441.

Synthesis of 6j: General procedure for the alkynylation of aldehydes 19 (Method B): Et_3N (0.79 mL, 13.0 equiv) was added to a solution of LiHMDS (1.0 M in toluene, 0.88 mL, 0.88 mmol, 2.00 equiv) at RT and the solution was cooled to −78 °C. A solution of alkyne **20** (169 mg, 0.880 mmol, 2.00 equiv) in toluene (20 mL) was added slowly with stirring and stirring was continued for 15 min at −78 °C and for 15 min at −60 °C; then, the mixture was allowed to warm to RT and stirred for an additional 1 h. After cooling the mixture again to −78 °C, a solution of aldehyde **19j** (100 mg, 0.440 mmol, 1.00 equiv) in toluene (10 mL) was added with stirring via syringe pump (1 mL h^{-1}) and stirring was continued for 1 h. After the addition had been completed, the mixture was allowed to warm to RT and the reaction quenched by addition of saturated NH_4Cl (aq.) solution (30 mL). The mixture was extracted with *t*BuOMe (3×50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe 10:1) to yield alcohol **6j** (114 mg, 62%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.78 (s, 1H), 2.00–1.87 (m, 2H), 2.27 (s, 3H), 2.80 (t, J=7.9 Hz, 2H), 4.48 (t, J=6.5 Hz, 1H), 6.98–6.93 (m, 4H), 7.10–7.02 (m, 3H), 7.32–7.26 (m, 3H), 7.33 (t, J=3.6 Hz, 1H), 7.47 ppm (dd, J=7.7, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=20.5, 31.2, 37.5, 62.3, 81.0, 94.9, 115.2, 118.1 (2C), 119.6, 123.0, 123.6, 124.1, 128.2, 129.6 (2C), 129.9, 130.2, 133.2, 133.7, 137.4, 137.6, 157.3, 157.4 ppm; IR (ATR): $\tilde{\nu}$=1589, 1483, 1443, 1250, 1221, 1160, 1038, 869, 749, 689 cm^{-1}; UV (MeCN): λ_{max} (lg ε)=199 nm (4.875), 252 (4.128), 271 (3.702), 278 (3.703); MS (ESI, MeOH): m/z (%): 443.1 (22) $[M+Na]^+$, 865.2 (100) $[2M+Na]^+$; HRMS (ESI): m/z calcd for $C_{24}H_{21}BrO_2$: 443.0617 $[M+Na]^+$, 445.0598 $[M+Na]^+$; found: 443.0604, 445.0592.

Synthesis of 7i: General procedure for the domino carbopalladation/C−H-activation reaction (Method A): A solution of propargylic alcohol **6i** (98.0 mg, 0.240 mmol, 1.00 equiv), nBu_4NOAc (205 mg, 0.720 mmol, 3.00 equiv), and LiOAc (50.0 mg, 0.960 mmol, 4.00 equiv) in DMF/MeCN/H_2O (5:5:1, 4.8 mL) was thoroughly degassed; then, the palladium catalyst (**10**; 20.5 mg, 24.0 μmol, 0.10 equiv) was added and the mixture was heated to 140 °C for 4 h under microwave irradiation. After cooling to RT and quenching with saturated NH_4Cl (aq.) solution (20 mL), the aqueous layer was extracted with *t*BuOMe (4×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (petroleum ether/*t*BuOMe, 5:1) to yield **7i** (16.0 mg, 49.0 μmol, 21%) as dark-yellow crystals. Method B: A solution of propargylic alcohol **6i** (47.0 mg, 0.115 mmol, 1.00 equiv), PPh_3 (33.0 mg, 0.121 mmol, 1.05 equiv), and K_2CO_3 (178 mg, 1.29 mmol, 11.2 equiv) in DMF (2.0 mL) was degassed thoroughly; then, $Pd(OAc)_2$ (6.00 mg, 23.0 mmol, 0.20 equiv) was added and the mixture was heated to 100 °C for 2 h under microwave irradiation. After cooling to RT and quenching by the addition of saturated NH_4Cl (aq.) solution (10 mL), the aqueous layer was extracted with *t*BuOMe (3×50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe, 3:1) to yield alkene **7i** (36.0 mg, 97%) as a yellow solid. M.p.: 154 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ=2.25 (ddt, J=20.5, 2.6, 6.7 Hz, 1H), 2.43 (ddt, J=7.9, 4.6, 7.3 Hz, 1H), 2.99 (t, J=7.1 Hz, 2H), 5.63 (dd, J=2.6, 4.4 Hz, 1H), 6.80 (ddd, J=1.4, 7.1, 7.8 Hz, 1H), 6.93 (m, 3H), 7.15–7.24 (m, 5H), 7.27 (m, 1H), 7.32 (m, 1H), 7.40 ppm (dd, J=1.5, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.4, 30.8, 65.2, 116.6 (2C), 122.4, 122.5, 122.9, 124.7, 125.1, 125.0, 127.4, 127.6, 128.1 (2C), 128.3, 128.9, 130.0, 134.2, 135.1, 139.5, 154.5, 154.7 ppm; IR (ATR): $\tilde{\nu}$=2923, 1594, 1445, 1248, 1200, 1115, 1098, 765, 742 cm^{-1}; UV (MeCN): λ_{max} (lg ε)=321 (3.805), 277 nm (3.857); MS (ESI, MeOH): m/z (%): 349.1 (67) $[M+Na]^+$, 675.2 (100) $[2M+Na]^+$; HRMS (ESI): m/z calcd for $C_{23}H_{18}O_2$: 349.1199 $[M+Na]^+$, 350.1233 $[M+Na]^+$; found: 349.1205, 350.1237.

Synthesis of alcohol (*S*)-6a: Oxidation of (*rac*)-6a: Dess–Martin periodinane (0.256 g, 0.606 mmol, 2.50 equiv) was added to a stirring solution of the racemic alcohol (*rac*)-**6a** (0.101 g, 0.240 mmol, 1.00 equiv) in dry CH_2Cl_2 (10 mL) under an argon atmosphere. The reaction mixture was stirred for 24 h at RT. After removal of the solvent, the crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe, 5:1) to yield the propargylic ketone as a brown oil (116 mg, quant). ^{1}H NMR (600 MHz, $CDCl_3$): δ=4.72 (s, 2H), 6.72 (dd, J=8.2, 1.2 Hz, 1H), 6.84 (td, J=7.5, 1.0 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.99 (dd, J=9.7, 2.0 Hz, 2H), 7.09 (t, J=7.6 Hz, 1H), 7.13 (t, J=7.4 Hz, 1H), 7.17–7.22 (m, 1H), 7.32–7.36 (m, 2H), 7.36- 7.40 (m, 1H), 7.50 (dd, J=7.9, 1.5 Hz, 1H), 7.58 ppm (dd, J=7.7, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=74.1, 89.7, 91.7, 111.3, 112.3, 118.2, 119.2 (2C), 122.9, 123.2, 124.1, 128.4, 129.9 (2C), 132.9, 133.6, 135.3, 154.3, 156.2, 159.6, 182.2 ppm; IR (ATR): $\tilde{\nu}$=2194, 1685, 1666, 1587, 1475, 1443, 1224, 1029, 744 cm^{-1}; UV (MeCN): λ_{max} (lg ε)=197 (4.887), 281 (4.134), 315 nm (3.796); MS (ESI, MeOH): m/z (%): 431.0 (12) $[M+Na]^+$, 837.0 (100) $[2M+Na]^+$; HRMS (ESI): m/z calcd for $C_{22}H_{15}BrO_3$: 429.0097 $[M+Na]^+$, 431.0077 $[M+Na]^+$; found: 429.0089, 431.0066.

Enantioselective transfer hydrogenation reaction: A mixture of the obtained propargylic ketone (20.0 mg, 49.0 μmol, 1.00 equiv) and the ruthenium catalyst (*R,R*)-**26** (2.6 mg, 4.90 μmol, 0.10 equiv) in *i*PrOH/MeOH (0.80/0.08 mL) was stirred for 22.5 h at RT under an argon atmosphere. After removal of the solvent, the crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe, 5:1) to yield the propargylic alcohol (*S*)-**6a** as a brown oil (20.0 mg, 99%). HPLC: Chiralcel OD, eluent: *i*PrOH/*n*-hexane(10:90), flow rate 0.8 mL min^{-1}, 95% *ee*. α_D^{20}=+15.29. All other characterization data were consistent with the racemic mixture.

Synthesis of (*S*)-7a: A solution of propargylic alcohol (*S*)-**6a** (15.5 mg, 37.9 μmol, 1.00 equiv), PPh_3 (10.0 mg, 37.9 μmol, 1.00 equiv), and K_2CO_3 (58.0 mg, 0.424 mmol, 11.2 equiv) in DMF (1.0 mL) was thoroughly degassed and then $Pd(OAc)_2$ (2.0 mg, 7.5 μmol, 0.20 equiv) was added. The reaction mixture was heated at 100 °C for 2 h under microwave irradiation. After cooling to RT and quenching by addition of saturated NH_4Cl (aq.) solution (10 mL), the mixture was extracted with *t*BuOMe (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/*t*BuOMe, 3:1) to yield (*S*)-**7a** as a yellow solid (9.2 mg, 74%). HPLC analysis: Chiralcel OD, eluent: *i*PrOH/*n*-hexane (5:95), flow rate 0.8 mL min^{-1}, 95% *ee*. All other characterization data were consistent with the racemic mixture.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft, the Center for Material Crystallography, and the Fonds der Chemischen Industriefor their generous support.

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Received: October 11, 2011
Published online: January 19, 2012

