JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

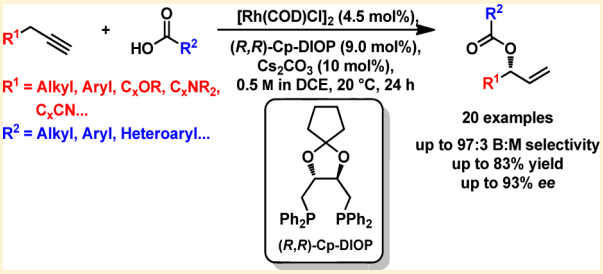
Enantioselective Redox-Neutral Rh-Catalyzed Coupling of Terminal Alkynes with Carboxylic Acids Toward Branched Allylic Esters

Philipp Koschker, Matthias Kähny, and Bernhard Breit*

Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Albertstraße 21, 79104 Freiburg im Breisgau, Germany

Supporting Information

ABSTRACT: We report on the first enantioselective variant of the atom-economic and redox-neutral coupling of carboxylic acids with terminal alkynes under rhodium catalysis utilizing the chiral, bidentate (*R*,*R*)-Cp-DIOP ligand. This represents the first example of this convenient asymmetric access to valuable branched allylic esters. The utility of this methodology is demonstrated by both a reaction performed on large scale and a short three-step synthesis of two naturally occurring γ-butyrolactones. A stereochemical model explaining the observed absolute configuration of the products based on DFT calculations is given.

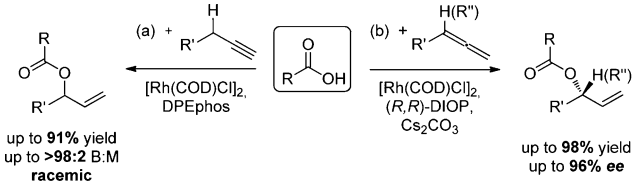


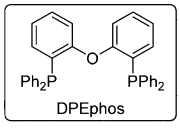
1. INTRODUCTION

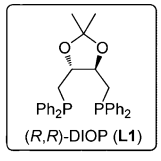
The branched allylic ester moiety is a common functionality found in numerous complex molecules.[1] Additionally, the possibility for subsequent transformations of allylic alcohols and their derivatives adds to the attractiveness of allylic esters as a substrate class.[2] While various transition-metal-catalyzed methods toward their synthesis have been developed over the past years,[3−6] they rarely address atom economy,[7] and asymmetric procedures still remain sparse. Functionalization via addition of (pro-)nucleophiles to alkynes[8] or allenes[9] can meet both of these requirements for the synthesis of various carbon- or hetereo-functionalized allylic compounds. However, this chemistry is still remarkably underdeveloped in the case of allylic esters.[10]

We recently developed a methodology for the preparation of branched allylic esters starting from terminal alkynes employing a Rh(I)/DPEphos catalyst system (Scheme 1a), which operates both inter- and intramolecularly.[11] The reaction does not require any stoichiometric reagents and was therefore the first example of an atom economic approach toward the desired substrate class. However, the construction of a new stereocenter makes the development of a truly economic, asymmetric variant desirable. Preliminary results, when exchanging the DPEphos ligand for the chiral (*R*,*R*)-DIOP ligand without further optimization, were also reported and led to the enantioenriched branched allylic ester in <50% conversion with both low regio- and enantioselectivity (see also Table 1, entry 1). Although these results were unsatisfactory, they demonstrated the theoretical potential for an asymmetric reaction with such a catalyst system.

Scheme 1. Previous Results for the Coupling with Alkynes Using Rh(I)/DPEphos and with Allenes Using Rh(I)/(*R*,*R*)-DIOP







Based on the assumption that this reaction proceeds via the initial isomerization to the corresponding allene intermediate, we were also able to develop a highly enantioselective coupling starting directly from terminal allenes, thus yielding the branched esters based on the aforementioned Rh(I)/(*R*,*R*)-DIOP catalyst system (Scheme 1b).[12] This offers an interesting alternative route toward the desired ester products. However, allenes as a substrate class are still relatively uncommon, lessening the general appeal of the reaction. Only few allene substrates are commercially available, and many syntheses of allenes start from the corresponding alkyne.[13] Furthermore, allenes appear much less frequently as intermediates in synthesis than alkynes. Therefore, our research focused on the development of an asymmetric coupling starting directly from alkynes (Scheme 2).

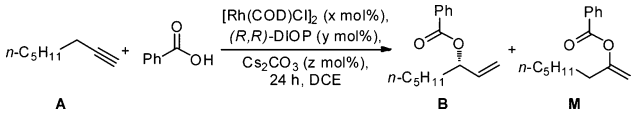
2. RESULTS AND DISCUSSION

The preliminary results for the Rh(I)/(*R*,*R*)-DIOP catalyst system mentioned above were promising enough to warrant

Received: February 2, 2015
Published: February 10, 2015

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137

Table 1. Condition Screening with the Rh(I)/(*R*,*R*)-DIOP Catalyst System[a]

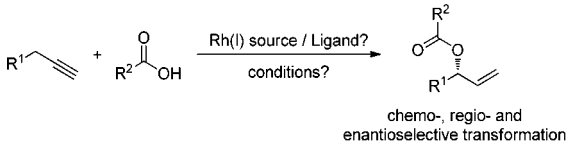


A B M

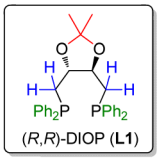
no.	*x*	*y*	*z*	*A* (equiv)	*c* (M)	*T*(°C)	conv. (%)[b]	**B:M**[c]	ee (%)[d]
1	2.5	5.0	–	2.0	0.1	70	42	80:20	68
2	2.5	5.0	–	2.0	0.1	50	20	85:15	74
3	2.5	5.0	5.0	2.0	0.1	50	42	89:11	71
4	2.5	5.0	5.0	2.0	1.0	50	85	86:14	68
5	2.5	5.0	5.0	2.0	1.0	40	64	89:11	78
6	2.5	5.0	5.0	2.0	1.0	30	41	90:10	82
7	2.5	5.0	5.0	1.5	1.0	30	32	90:10	77
8	2.5	5.0	5.0	1.0	1.0	30	25	90:10	70
9	2.5	5.0	5.0	2.0	1.0	20	17	89:11	85
10	2.5	5.0	10	2.0	0.5	20	30	92:8	85
11	4.5	9.0	10	2.0	0.5	20	83	94:6	85

[a]A screw-cap flask was charged with $[Rh(COD)Cl]_2$, (*R*,*R*)-DIOP, 0.44 mmol benzoic acid, and 1,2-dichloroethane. 1-octyne was added, and the mixture set to the reaction temperature and stirred for 24 h. [b]Determined by integration of the aromatic signals in the crude ^{1}H NMR spectrum. [c]Determined by integration of the olefinic protons in the crude ^{1}H NMR spectrum. [d]Determined by chiral HPLC.

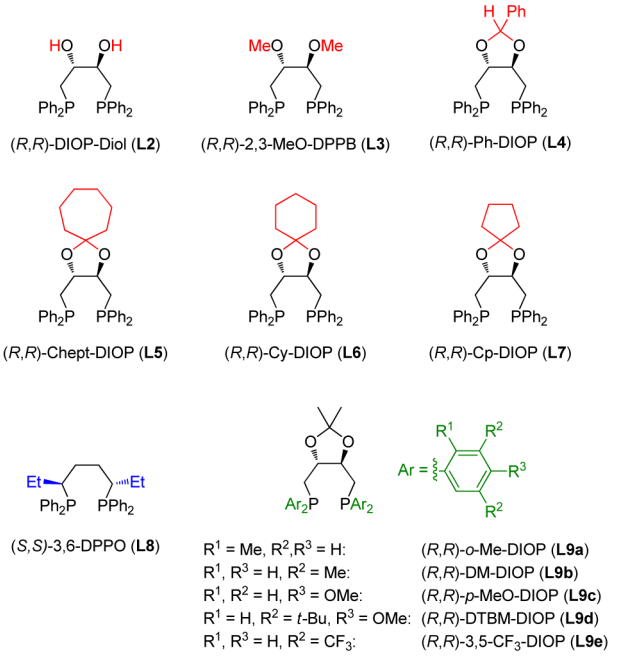
Scheme 2. Desired Enantioselective Coupling of Terminal Alkynes with Carboxylic Acids



Scheme 3. Newly Synthesized Bidentate Ligands (Formally) Derived from DIOP (L1)



(*R*,*R*)-DIOP (**L1**)



further investigation.[11] We performed an optimization of the reaction parameters starting from the conditions for the racemic methodology. This is depicted in Table 1.

Starting from the aforementioned conditions (entry 1), both enantio- and regioselectivity could be improved by lowering the reaction temperature, although the conversion dropped significantly. The loss in reactivity could partially be compensated by using catalytic amounts of Cs_2CO_3 as a base (entry 3) and running the reaction at higher concentrations (entry 4). Unfortunately, lowering the ratio of alkyne to carboxylic acid resulted in lower conversions as well as lower enantioselectivities (entry 6–8). This is in line with previous results for the racemic coupling with DPEphos where 2.0 equiv of alkyne was required as well.[11] The second equivalent of alkyne seems however to only be necessary for the release of the product during the reaction and can be partially reisolated afterward, if required.[14] The best reaction conditions were found at 20 °C when increasing the amount of both the catalyst and Cs_2CO_3 (entry 11). In this case, the concentration had to be lowered again to 0.5 M due to solubility problems of both the acid and the catalyst at lower temperatures. Although the optimization of the catalysis with (*R*,*R*)-DIOP (**L1**) led to significant improvements over the previous preliminary results, neither full conversion of the substrates nor very high enantioselectivities in the range of >90% ee could be achieved. Furthermore, the purification of the product in case of the optimized conditions led to an isolated yield of only 73%.

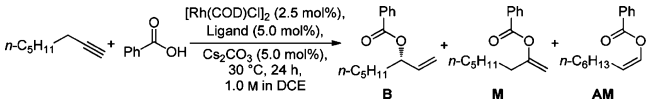
Since these results were not satisfying for a general methodology, several ligands based on the DIOP structure were synthesized analogous to the literature-known synthesis[15] of the simple DIOP ligand (Scheme 3) and screened.[16]

One of the main advantages of DIOP is that it offers numerous options for derivatization.[17] Several synthesized ligands differ from the general DIOP structure via alteration of the acetal backbone, either by opening the ring (**L2**, **L3**) or by changing it for a different cyclic acetal. Both non-C2 symmetrical (**L4**) and C2-symmetrical derivatives (**L5**, **L6**, **L7**) were tested. Additionally, a formal derivative bearing the chirality in the α-position to the phosphorus was synthesized (**L8**). Several ligands with different substituents on the aromatic moiety displaying varying steric and electronic properties (**L9a-e**) were prepared and tested as well. All DIOP derivatives were

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137

screened utilizing the conditions given in Table 1, entry 6, because the completely optimized conditions increased the difficulty of recognizing incremental improvements. The results are given in Table 2.

Table 2. Ligand Screening and Comparison for Optimized DIOP Conditions[a]



no.	ligand	conv. (%)[b]	B:M:AM[c]	ee (%)[d]
1	(*R*,*R*)-DIOP (**L1**)	41	90:10:–	82
2	(*R*,*R*)-DIOP-Diol (**L2**)	5	25:75:–	–
3	(*R*,*R*)-2,3-MeO-DPPB (**L3**)	35	83:17:–	32
4	(*R*,*R*)-Ph-DIOP (**L4**)	23	81:19:–	86
5	(*R*,*R*)-Chept-DIOP (**L5**)	40	89:11–	81
6	(*R*,*R*)-Cy-DIOP (**L6**)	37	89:11:–	80
7	(*R*,*R*)-Cp-DIOP (**L7**)	45	92:8:–	85
8	(*S*,*S*)-3,6-DPPO (**L8**)	15	75:22:3	−73
9	(*R*,*R*)-*o*-Me-DIOP (**L9a**)	11	35:10:55	–
10	(*R*,*R*)-DM-DIOP (**L9b**)	11	83:17:–	75
11	(*R*,*R*)-*p*-MeO-DIOP (**L9c**)	10	87:13:–	70
12	(*R*,*R*)-DTBM-DIOP (**L9d**)	traces	–	–
13	(*R*,*R*)-3,5-CF_3-DIOP (**L9e**)	16	90:10:–	34
14[e]	(*R*,*R*)-Cp-DIOP (**L7**)	>95	94:6:–	90
15[e]	(*R*,*R*)-DIOP (**L1**)	83	94:6:–	85

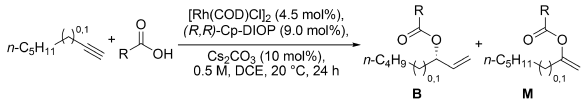
[a]A screw-cap flask was charged with $[Rh(COD)Cl]_2$, ligand, 0.44 mmol of benzoic acid and 1,2-dichloroethane. 0.88 mmol of 1-octyne was added, and the mixture set to the reaction temperature and stirred for 24 h. [b]Determined by integration of the aromatic signals in the crude ^{1}H NMR spectrum. [c]Determined by integration of the olefinic protons in the crude ^{1}H NMR spectrum. [d]Determined by chiral HPLC; [e]Optimized conditions from Table 1, entry 11 (4.5 mol % $[Rh(COD)Cl]_2$, 9.0 mol % ligand, 10 mol % Cs_2CO_3, 20 °C, 0.5 M).

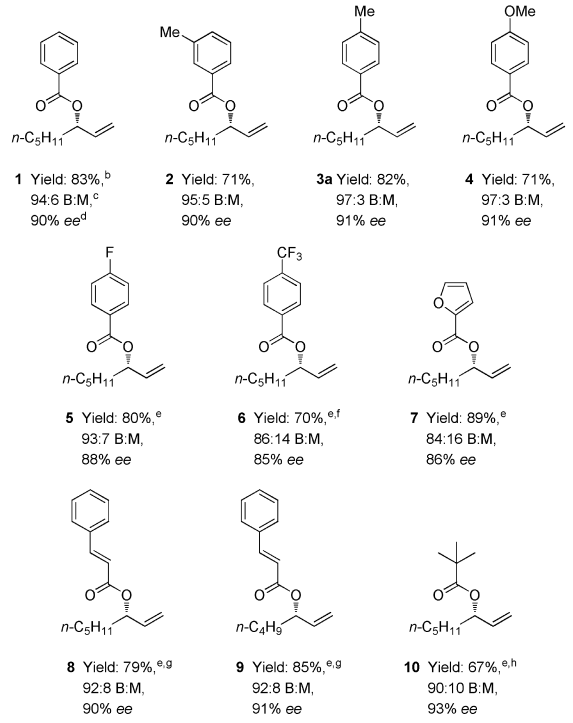
In general, the screening reconfirmed the DIOP ligand class as potentially suitable for the coupling reaction. It has been previously suggested that the similar bite angles of DIOP and DPEphos might serve as an explanation for the potency of these ligands in this transformation.[11,12,18] The only ligands tested that did not yield any significant amount of product were (*R*,*R*)-DIOP-Diol (**L2**), with an apparently large effect of the free hydroxyl functions and the more sterically hindered ligands, (*R*,*R*)-*o*-Me-DIOP (**L9a**) and (*R*,*R*)-DTBM-DIOP (**L9d**). The enantioselectivity was lowered in cases of acyclic backbones (**L3** and **L8**) as well as for the electron-poor (*R*,*R*)-3,5-CF_3-DIOP (**L9e**). (*R*,*R*)-Cp-DIOP (**L7**) was found to give both slightly better regio- and enantioselectivity as well as a higher conversion. After applying this ligand to the previous best results for (*R*,*R*)-DIOP (**L1**, entry 15), the desired product could be obtained with complete conversion, an excellent **B**:**M** ratio of 94:6 and the highest enantioselectivity (entry 14).

These results were a general improvement over those obtained with (*R*,*R*)-DIOP (**L1**), showing approximately 20% higher conversions as well as an increase in enantioselectivity from 85% ee to 90% ee. This was considered significant enough to continue our investigations of the substrate scope with the new ligand. It should be noted, however, that the commercially available (*R*,*R*)-DIOP ligand does work for this chemistry, making the methodology more appealing for actual applications in synthesis.

Utilizing the optimized reaction conditions (Table 2, entry 14), we first investigated the scope of the carboxylic acid reaction partner, using 1-octyne as the standard substrate (Table 3). We were pleased to find that the desired branched

Table 3. Scope of the Carboxylic Acid Coupling Partner with 1-Octyne (and 1-Heptyne)[a]





[a]An 1 mL screw-cap flask was charged with 0.020 mmol $[Rh(COD)Cl]_2$, 0.040 mmol (*R*,*R*)-Cp-DIOP, 0.044 mmol Cs_2CO_3, 0.44 mmol of acid and 0.88 mL 1,2-dichloroethane, cooled to 20 °C. 0.88 mmol of alkyne was added, and the reaction stirred for 24 h. [b]Isolated yields of pure B product, unless otherwise noted. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC. [e]Isolated yield of **B**:**M** mixture. [f]80% conversion. [g]Performed at 15 °C. [h]Performed at 25 °C, 75% conversion.

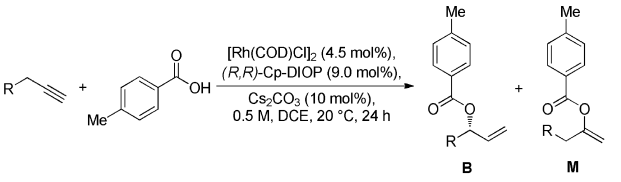
allylic ester products could be isolated in good to very good yields with high regioselectivities of up to 97:3. The given enantioselectivities were especially impressive in comparison to the corresponding coupling of linear allenes, which was only in the range of 80% ee.[12] In addition to benzoic acid (**1**), different substituted benzoic acid derivatives were also applied successfully. Both electron-rich and electron-poor derivatives with substituents in different positions reacted to the desired products (**2**–**6**), though there appears to be a trend of slightly lessened enantioselectivity as well as **B**:**M** selectivity when the substituent is more electron-withdrawing. As an example for heteroaromatic acids, 2-furanoic acid was coupled in good yields, though both regio- and enantioselectivity were slightly lowered to 84:16 and 86% ee, respectively (**7**). The coupling of cinnamic acid with both 1-ocytne and 1- heptyne led to the desired products with good yields and selectivities (**8** and **9**), making this coupling especially interesting, which will be demonstrated below. We were also pleased to find that pivalic

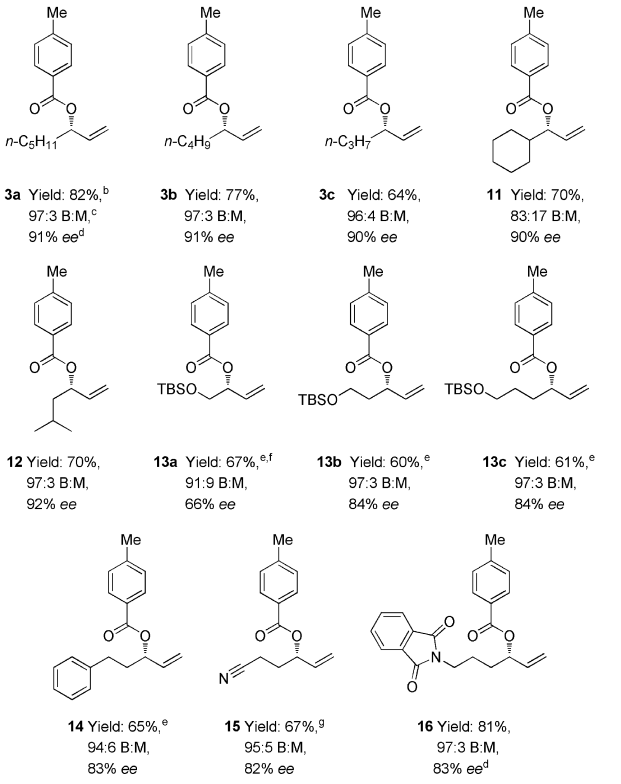
DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137

acid as an example for an aliphatic acid worked as well (**10**), though higher temperatures were needed, yielding the branched ester with high selectivities and the highest observed enantioselectivity. This might be due to the increased steric demand of the substrate. Higher reaction temperatures for aliphatic acids were also necessary for the allene coupling,[12] giving further evidence that both couplings might proceed via the same mechanism in regard to the second part of the catalysis (see Scheme 6).

Next, we investigated the scope of the alkyne partner (Table 4) using *p*-methylbenzoic acid as the standard substrate, which

Table 4. Scope of the Terminal Alkyne Coupling Partner with *p*-Methylbenzoic Acid[a]



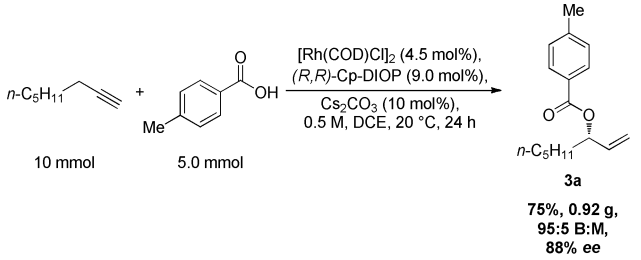


[a]An 1 mL screw-cap flask was charged with 0.020 mmol [Rh(COD)-Cl]$_2$, 0.040 mmol (*R*,*R*)-Cp-DIOP, 0.044 mmol Cs_2CO_3, 0.44 mmol of acid and 0.88 mL 1,2-dichloroethane, cooled to 20 °C. 0.88 mmol of alkyne was added, and the reaction stirred for 24 h. [b]Isolated yields of pure B product, unless otherwise noted. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC. [e]70% conversion. [f]Isolated yield of **B**:**M** mixture. [g]75% conversion.

gave the best results in regard to both yield and enantioselectivity (Table 3, **3a**). The utility of this methodology for the coupling with linear aliphatic alkynes was demonstrated with all three substrates resulting in excellent regio- and enantioselectivity and good yields (**3a**–**c**). Branching in the homopropargylic position had no effect on either yield or enantioselectivity (**11**). However, the increased steric demand seems to impact the β-hydride elimination leading to the intermediate allene. This means that the regioselectivity was lowered and more byproduct **M** formed. This effect was not observable with additional space between the propargylic position and the branching (**12**). We were also pleased to find that different functional groups such as a TBS-protected alcohol with different distances from the allylic position (**13a**–**c**), a phenyl substituent (**14**), a terminal nitrile (**15**), or a phthalimide-protected amine (**16**) were all tolerated in the reaction, giving the desired products with good regio- and enantioselectivity.[19,20] However, in some cases the yields were slightly lower, partially due to solubility problems of the alkynes in the concentrated DCE reaction mixture, which led to incomplete conversions (~70%) (**13**–**15**). Surprisingly, a TBSO-group in homopropargylic position led to significantly lower enantioselectivities (**13a**), an effect that cannot be observed with TBSO-groups further from the propargylic position.

To demonstrate the synthetic utility on a larger scale, the optimized reaction between *p*-methylbenzoic acid and 1-octyne was performed on a 5.0 mmol scale (Scheme 4), giving the pure

Scheme 4. Coupling Between 1-Octyne and *p*-Methylbenzoic Acid on a 5.0 mmol Scale



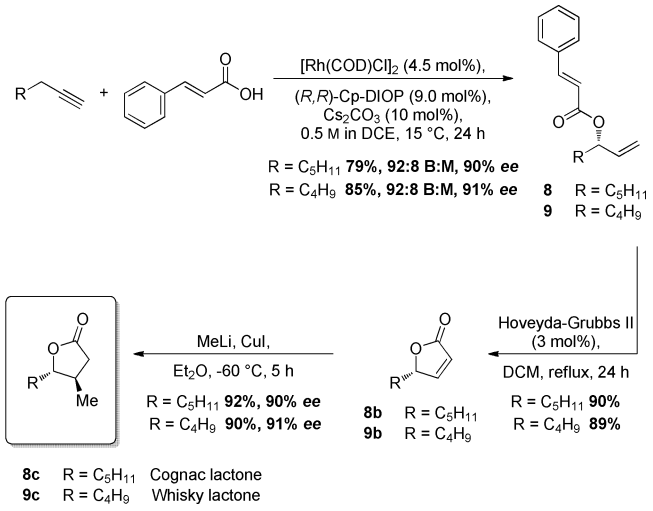
branched ester in 0.92 g (75% yield). The product was formed in a 95:5 **B**:**M** ratio and could be isolated pure after standard column chromatography. The upscaling only had a slight impact on the enantioselectivity with a still high value of 88% ee.

The higher enantioselectivities for linear aliphatic alkynes as seen in Table 3 and 4 gave reason to revisit the synthesis of naturally occurring γ-butyrolactones.[21] Both *trans*-cognac lactone (**8c**) and *trans*-whisky lactone (**9c**) were synthesized in good overall yields of 60% and 63% and with high enantioselectivities of 90% ee and 91% ee, respectively, over three short steps starting from cinnamic acid and the corresponding alkynes (Scheme 5). The mixture of the purified branched and vinyl ester products in the first step of the synthesis was used in the next steps without further separation on $AgNO_3$-impregnated silica gel, because a separation after the final step of the synthesis was more convenient. Following the Rh-catalyzed coupling reaction, the synthesis was completed by a ring closing metathesis and a subsequent Michael addition of the cuprate Me_2CuLi. Both steps followed literature procedures and gave perfect selectivity as well as very good yields.[22] As expected, the enantiomeric excess established during the coupling reaction was unaffected by the following steps.

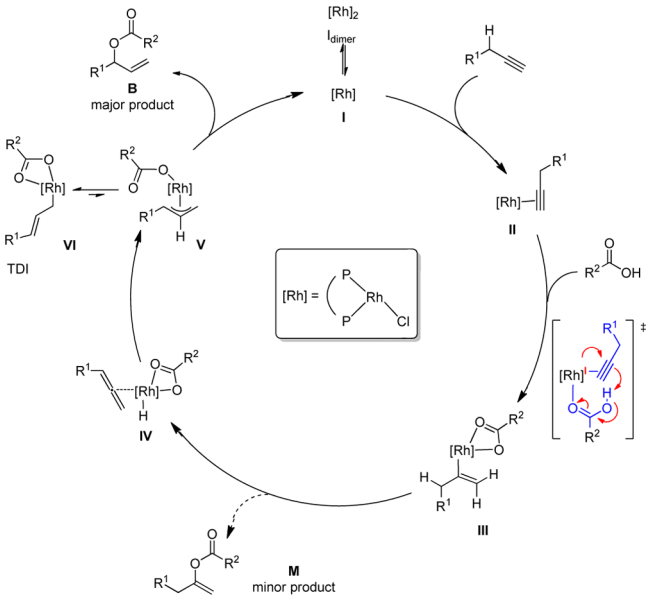
Our group has recently published detailed mechanistic investigations for the reaction, giving insight on the currently prevailing mechanism for the racemic coupling (Scheme 6).[23] The catalyst enters the cycle as the monomeric Rh(I) species **I**, which first coordinates the alkyne leading to the complex **II**.

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131–3137

Scheme 5. Enantioselective Synthesis of *trans*-Cognac Lactone (8c) and *trans*-Whisky Lactone (9c)



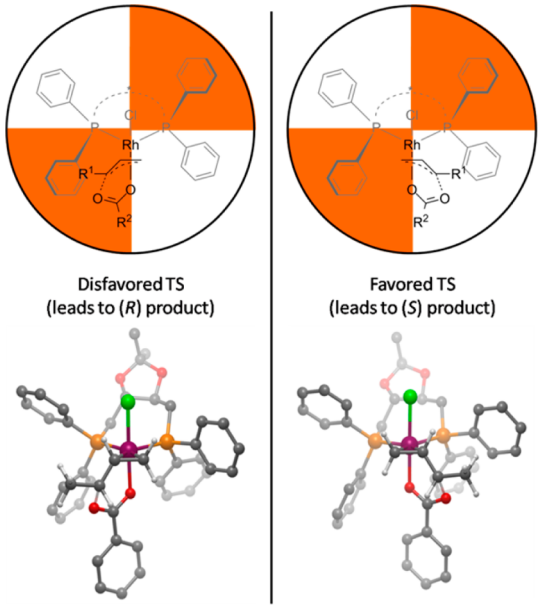
Scheme 6. Mechanism for the Coupling of Terminal Alkynes with Carboxylic Acids Based on Mechanistic Investigations and DFT Calculations



The following coordination of the carboxylic acid results in the formation of a hydrogen bond between the C_{sp} center and the OH group of the acid. An intramolecular protonation leads to the vinyl-Rh species **III**. This complex can either undergo reductive elimination to the observed Markovnikov byproduct **M** or β-hydride elimination toward the intermediate rhodium hydride species **IV**. A hydrometalation step leads to the Rh-π-allyl complex **V**, which releases the branched allylic ester **B** by reductive elimination, reforming the Rh(I) species **I**. An equilibrium of the Rh-π-allyl species **V** with the complex **VI** as a resting state explains why long reaction times are necessary. When starting from the corresponding allene substrate, the catalytic cycle begins with the formation of complex **IV**. This serves as an explanation for the absence of side products with allenes, because the precursor for the **M** product, complex **III**, is not formed during the catalysis.

In order to develop a rational for the observed asymmetric induction, we exchanged the DPEphos ligand within the DFT-calculated mechanism with (*R*,*R*)-DIOP and optimized the structures of the transition states with benzoic acid and 1-butyne leading to the (*R*) and the (*S*) product, respectively (Scheme 6, from **V** to **B**).[24] These calculations allowed for the proposal of a stereochemical model based on Knowles' quadrant model (Scheme 7),[25] which can serve as a possible

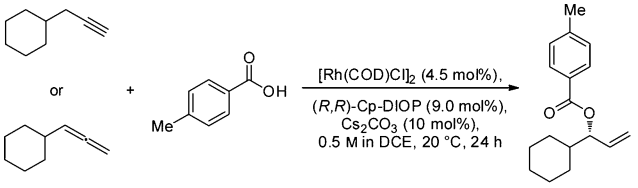
Scheme 7. Model Explaining the Observed Stereochemistry Based on the DFT-Calculated Optimized Transition-State Structures (BP86/def2SVP)[26,27]



explanation for the experimentally observed (*S*) configuration of the product: When using (*R*,*R*)-DIOP, two quadrants at the metal center are blocked by the aromatic rings of the ligand. This makes it energetically favored for the carboxylate as well as for the substituent on the π-allyl to reach into the larger available space offered by the less sterically hindered quadrants. Based on this model the formation of the (*S*) branched allylic ester is favored, which is in agreement with the absolute configuration generally observed in this methodology.

As a confirmation of the proposition that both alkyne and allene coupling proceed via the same mechanism, we compared both reactions with corresponding allene and alkyne substrates under identical reaction conditions, leading to the same branched allylic ester product (Scheme 8). The result for the

Scheme 8. Comparison Between the Coupling of *p*-Methylbenzoic Acid with Cyclohexyl Allene and 3-Cyclohexyl-1-Propyne, Respectively



from alkyne: Yield: **70%**, **83:17 B:M**, **90% *ee***

from allene: Yield: **92%**, **100:0 B:M**, **82% *ee***

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137

alkyne coupling was taken from Table 4. Both coupling reactions led to the same product with the same absolute configuration. The lack of byproduct formation for the allene has already been elaborated upon during the discussion of the mechanism. The slight differences in yield and selectivity between the two reactions can possibly be explained by two differences. First, 2.0 equiv of the substrate are required for efficient product release in the alkyne coupling. Second, the alkyne reaction is slower due to the initial isomerization step. However, linear allene substrates led to significantly lower enantioselectivities than the corresponding alkynes. This might not be explainable with the currently prevailing mechanistic understanding of this reaction and will therefore be addressed in future investigations, in particular for the allene coupling.

3. CONCLUSION

In summary, the newly developed methodology is the first example of a direct asymmetric redox-neutral coupling of terminal alkynes with carboxylic acids leading to highly attractive branched allylic esters. The products are formed in moderate to good yields with high enantio- and regioselectivities, displaying a relatively broad functional group tolerance. The fact that this reaction yields products with aliphatic side chains with higher enantiomeric excess compared to the previously published allene coupling makes this methodology an interesting alternative: Depending on the structure of the desired products, both allene and alkyne coupling can now be used complementarily. A coupling performed on a 5.0 mmol scale led to good results, demonstrating the utility of this method in synthesis. As an application for this new reaction, the rapid formation of two natural products, cognac lactone and whisky lactone, which both display interesting biological properties,[28] was shown with high enantioselectivity. A model for the transition state of the reductive elimination step with (*R*,*R*)-DIOP, which is based on DFT calculations starting from our previous mechanistic investigations, serves as a possible explanation for the observed absolute configuration.

Future studies will focus on the intramolecular synthesis of macrolactones as well as the application of this methodology in the synthesis of more complex target structures.

4. EXPERIMENTAL SECTION

General Procedure for the Coupling of Terminal Alkynes and Carboxylic Acids. An 1.0 mL screw-cap flask[29] was flame-dried under vacuum, backfilled with argon (Argon 5.0 from Sauerstoffwerke Friedrichshafen) and cooled to room temperature using a standard Schlenk line apparatus. The screw-cap flask was charged with 0.020 mmol (9.80 mg) of $[Rh(COD)Cl]_2$, 0.040 mmol (21.0 mg) of (*R*,*R*)-Cp-DIOP, 0.044 mmol (14.3 mg) of Cs_2CO_3, and 0.44 mmol of acid. After the addition of the solids, the flask was evacuated and backfilled with argon three more times. 0.88 mL of freshly distilled 1,2-dichloroethane (DCE) were added under a flow of argon, and the resulting suspension cooled to 20 °C in a cooling bath. After stirring for 5 min at 20 °C, 0.88 mmol of alkyne was added under a flow of argon. The screw-cap flask was then sealed, and the mixture stirred for 24 h at 20 °C. The reaction mixture was directly flushed through a plug of silica gel and washed several times with dichloromethane. The light-yellow solution was concentrated under vacuum, and the crude mixture analyzed by ^{1}H NMR spectroscopy and purified by flash chromatography on silica gel. In cases of incomplete purification by regular flash chromatography, the purified products were chromatographed again for HPLC measurement on silica gel impregnated with $AgNO_3$ to separate the allylic esters **B** from the Markovnikov byproducts **M**.

General Procedure for the Ring Closing Metathesis of Cinnamic Ester Products.[22] A 10 mL screw-cap flask was flame-dried under vacuum, backfilled with argon, and cooled to room temperature. Hoveyda-Grubbs II (11 mg, 3.0 mol %) was added, and the flask was evacuated and backfilled with argon three times. A solution of the allylic ester in DCM (0.2 M) was added under a flow of argon, and the flask sealed. The reaction mixture was heated to 40 °C for 24 h. After removal of the solvent, the crude reaction mixture was purified by flash chromatography on silica gel (*n*-pentane:Et_2O 2:1) to give the pure product.

General Procedure for the Cuprate Addition Toward γ-Butyrolactones.[22] A solution of MeLi in Et_2O (1.6 M, 10 equiv) was added dropwise to a suspension of CuI (0.1 M, 5 equiv) in Et_2O at −20 °C. The reaction mixture was cooled to −60 °C, and a solution of the substrate in Et_2O (0.1 M) was added dropwise. After stirring for 5 h at −60 °C, the reaction was stopped via the addition of aqueous HCl (1 M) and filtered over Celite. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic solution was washed with sat. $NaHCO_3$ (10 mL), dried over Na_2SO_4, and the solvent removed. The crude product was purified by flash chromatography on silica gel (*n*-pentane:Et_2O 3:1) to give the pure lactone.

DFT calculations. Structure optimizations have been performed with the Gaussian 09 program,[30] using the BP86[26] functional in combination with the def2SVP[27] basis set. Single point energies have been calculated on the M06[31]/def2SVP level of theory using the IEFPCM model to account for solvent effects with the standard parameters for 1,2-DCE.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for synthesized ligands, alkynes, branched allylic esters and lactones, including ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR, and HPLC data sheets as well as further information on the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*bernhard.breit@chemie.uni-freiburg.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038), the Fonds der Chemischen Industrie, the Krupp Foundation. We thank Umicore, BASF, and Wacker for generous gifts of chemicals.

■ REFERENCES

(1) For examples of enantioenriched allylic esters in synthesis, see: (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774. (b) Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695. (c) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (d) Schotes, C.; Ostrovskyi, D.; Senger, J.; Schmidtkunz, K.; Jung, M.; Breit, B. *Chem.—Eur. J.* **2014**, *20*, 2164.

(2) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890.

(3) For palladium-catalyzed reactions see: (a) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320. (b) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Cannon, J. S.; Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 15185. (e) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448.

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137

(4) For iridium-catalyzed reactions see: (a) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* **2011**, *133*, 2072. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (c) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928. (d) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918. (e) Sharma, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 17983.

(5) For rhodium-catalyzed reactions see: (a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882. (b) Evans, P. A.; Leahy, D. K.; Slieker, L. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3613.

(6) For ruthenium and copper-catalyzed reactions see: (a) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047. (b) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567. (c) Andrus, M. B.; Zhou, Z. *J. Am. Chem. Soc.* **2002**, *124*, 8806. (d) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. (e) Onitsuka, K.; Okuda, H.; Sasai, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1454. (f) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206. (g) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.

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

(8) For addition reactions of C- and Het-nucleophiles on alkynes see: (a) Trost, B. M.; Brieden, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335. (b) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622. (c) Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 16124.

(9) For addition reactions of C- and Het-nucleophiles on allenes see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. (c) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (d) Trost, B. M.; Jäkel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (e) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537. (f) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (g) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (h) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166. (i) Kawamoto, T.; Hirabayashi, S.; Guo, X.-X.; Nishimura, T.; Hayashi, T. *Chem. Commun.* **2009**, 3528. (j) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (k) Toups, K. L.; Widenhoefer, R. A. *Chem. Commun.* **2010**, *46*, 1712. (l) Alcaide, B.; Almendros, P. *Adv. Synth. Catal.* **2011**, *353*, 2561. (m) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287. (n) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (o) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862. (p) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162. (q) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268. (r) Li, C.; Kähny, M.; Breit, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 13780.

(10) (a) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. (b) Kim, I. S.; Krische, M. J. *Org. Lett.* **2008**, *10*, 513.

(11) (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (b) Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789.

(12) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746.

(13) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.

(14) The crude ^{1}H NMR spectra show remaining alkyne substrate after finished reaction. The alkynes used for this methodology are inexpensive, and therefore reisolation was considered irrelevant. Nevertheless, trying to reisolate the alkyne after the coupling of 1-octyne with *p*-methylbenzoic acid resulted in 0.7 equiv of the alkyne being reisolated.

(15) (a) Dang, T. P.; Kagan, H. B. *Chem. Commun.* **1971**, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(16) Ligands in Table 1 are a selection of the ligands screened and/or synthesized. Most standard classes of chiral ligands commercially available were screened unsuccessfully, with good results exclusively for ligands with a C_4 backbone.

(17) For examples of DIOP derivatization see: (a) Dang, T. P.; Poulin, J.-C.; Kagan, H. B. *J. Organomet. Chem.* **1975**, *91*, 105. (b) Hobbs, C. F.; Knowles, W. S. *J. Org. Chem.* **1981**, *46*, 4422. (c) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871. (d) Yan, Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 4137. (e) Guiu, E.; Caporali, M.; Muñoz, B.; Müller, C.; Lutz, M.; Spek, A. L.; Claver, C.; van Leeuwen, P. W. N. M. *Organometallics* **2006**, *25*, 3102.

(18) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

(19) Unfortunately, a reaction with 5-hydroxy-1-pentyne as the alkyne substrate resulted in the desired product with <40% conversion (97:3 **B**:**M** ratio). A protection of the alcohol seems to be important in this chemistry in order to achieve higher conversions.

(20) Additionally, 3-phenyl-1-propyne was tested in the reaction, giving the desired allylic ester only in very low conversion (<10%) and with no enantiomeric excess. As a side reaction homocoupling of the alkyne was observed.

(21) For reviews on γ-butyrolactones and derivatives see: (a) Alali, F. W.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285. (c) Murcia, M. C.; Navarro, C.; Moreno, A.; Csákÿ, A. G. *Curr. Org. Chem.* **2010**, *14*, 15.

(22) Mao, B.; Geurts, K.; Fananás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948.

(23) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.-J.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 1097.

(24) For detailed information on the DFT calculations, see Supporting Information.

(25) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(26) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824.

(27) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305.

(28) (a) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.* **1992**, *33*, 4931. (b) Benedetti, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; Vicario, M. *Tetrahedron: Asymmetry* **2001**, *12*, 505.

(29) The kind of flask used is important for a successful reaction. It appears that the reaction is very sensitive to air, and therefore the tighter seal utilizing a Teflon screw cap is essential. A picture of the kind of flasks used for this coupling can be found in the Supporting Information.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.;Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, rev. B.01; Gaussian, Inc.: Wallingford, CT, 2010.

(31) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

DOI: 10.1021/jacs.5b01131
J. Am. Chem. Soc. 2015, 137, 3131−3137