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Highly Enantioselective Rh_2(*S*-DOSP)$_4$-Catalyzed Cyclopropenation of Alkynes with Styryldiazoacetates

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Abstract: Dirhodium tetrakis((*S*)-*N*-(dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$) is an effective catalyst for highly enantioselective cyclopropenation reactions between terminal alkynes and arylvinyldiazoacetates. The resulting vinylcyclopropenes can undergo rhodium-catalyzed regioselective rearrangement to cyclopentadienes. Computational studies indicate that the high enantioselectivity of the process is governed by the specific orientation of the alkyne during its approach to the carbenoid through a relatively late transition state. The specific orientation occurs due to the presence of a hydrogen bonding interaction between the alkyne hydrogen and a carboxylate ligand on the dirhodium catalyst.

Introduction

Chiral cyclopropenes are valuable intermediates in organic synthesis.[1] Their versatility has been demonstrated in a number of synthetically important transformations, including addition across the strained double bond,[2] transition metal-catalyzed cycloisomerization to heterocycles,[3] cycloadditions,[4] and metalation reactions.[5] Traditionally, methods utilized for cyclopropene synthesis have relied on elimination reactions from available cyclopropane precursors,[6] but enantioselective variants of this approach are not abundant.[7] An alternative way to prepare cyclopropenes is through the cyclopropenation of alkynes by metal carbenoids. Doyle et al. have demonstrated that, the chiral dirhodium(II) carboxamidate complex Rh_2(*S*-MEPY)$_4$, is an effective catalyst for enantioselective cyclopropenation reactions with diazoacetates.[8] Corey and co-workers have developed a mixed carboxylate/carboxamidate catalyst, Rh_2(OAc)(DPTI)$_3$, that was efficiently applied to similar cyclopropenation reactions.[9] Furthermore, a convenient approach to chiral cyclopropene synthesis via cyclopropenation, followed by diastereomeric and parallel kinetic resolution strategies, has been reported by Fox and co-workers.[10]

We have previously demonstrated that the dirhodium tetracarboxylate complex Rh_2(*S*-DOSP)$_4$ (**1**) is an effective chiral catalyst for enantioselective cyclopropenation reactions with aryldiazoacetates, generating cyclopropenes containing a quaternary stereocenter (Scheme 1).[11] Related studies by Chang et al. have shown that copper-catalyzed reactions of aryldiazoacetates with arylalkynes generate indenes.[12] During our earlier studies, the reactions between vinyldiazoacetates and phenylacetylene were unsuccessful.[11] In this paper, we describe a

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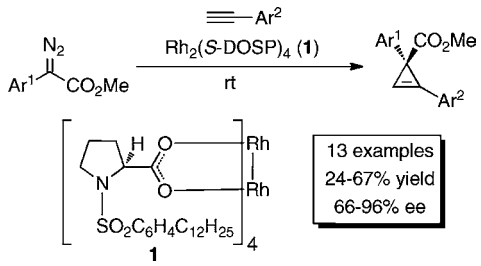
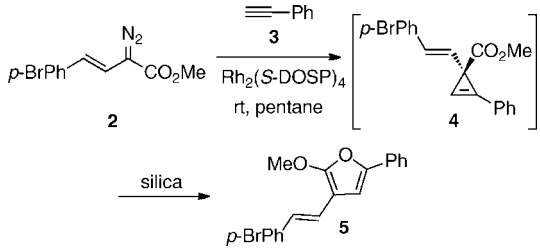
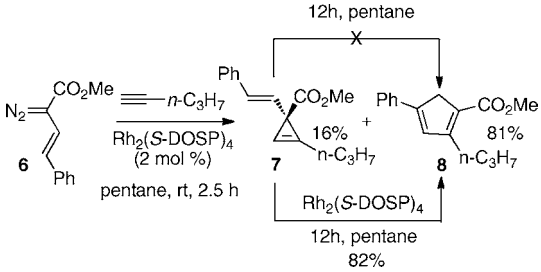
Scheme 1. Cyclopropenation with Aryldiazoacetates



Scheme 2. Formation of Furan **5**



Scheme 3. Cyclopropenation and Cyclopentadiene Formation



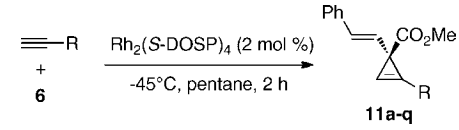
detailed study that re-examines this reaction because the resulting 3-vinylcyclopropenes would be useful intermediates.

Results and Discussion

The studies began by re-examining the reaction of vinyldiazoacetates with phenylacetylene. ^{1}H NMR analysis of the crude reaction mixture from the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of vinyldiazoacetate **2** with phenylacetylene (**3**) revealed that the cyclopropene **4** was indeed formed (Scheme 2). However, **4** was unstable on silica gel and readily rearranged to the furan derivative **5**, which was also unstable and decomposed upon standing at room temperature. The structure of **5** was tentatively assigned on the basis of NOE studies. These observations demonstrated that a cyclopropene could be formed from the reaction of vinyldiazoacetates with alkynes, but for the reaction to be broadly useful, more stabilized vinylcyclopropenes would need to be formed.

The study was extended to alkyl acetylenes, which would be expected to generate more stable cyclopropenes since they lack the phenyl donor-group. The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of 1-pentyne with methyl styryldiazoacetate **6** at room temperature gave a mixture of the cyclopropene **7** (16%) and the cyclopentadiene **8** (81%) (Scheme 3). Cyclopropene **7** was formed in high enantiomeric excess (98% ee) and appeared to be relatively stable. However, upon stirring overnight in the presence of Rh_2(*S*-DOSP)$_4$, rearrangement to **8** in 82% yield was observed. These results suggest that cyclopentadiene **8** is formed through a rhodium-catalyzed rearrangement of the initially formed cyclopropene **7**.

Table 1. Synthesis of Cyclopropenes **11**[a]

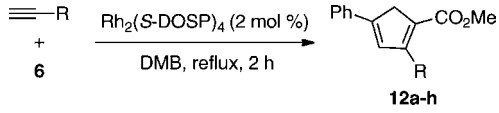


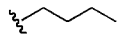
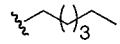
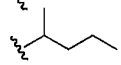
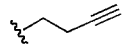
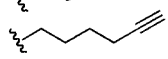
entry	R =	product	yield, %	ee, %
1		**11a**	81	99
2		**11b**	78	98
3		**11c**	85	99
4		**11d**	87	97
5		**11e**	78	97
6[b]		**11f**	72	98
7		**11g**	82	96
8		**11h**	76	98
9		**11i**	62	97
10	Ph	**11j**	89	95
11	Ph	**11k**	75	98
12[c]	Nap	**11l**	68	99
13		**11m**	46	96
14		**11n**	89	97
15	OTBS	**11o**	68	98
16	OTBS	**11p**	77	97
17	TMS	**11q**	85	99

[a] All reactions were performed by addition of the diazo compound (1.0 mmol) in 10 mL of pentane over 2 h to a stirred solution of alkyne (0.5 mmol) and catalyst (0.01 mmol) in 1 mL of pentane. [b] Methyl (*p*-trifluoromethyl)phenylvinyldiazoacetate was used. [c] Methyl (*p*-bromophenyl)vinyldiazoacetate was used.

Milder reaction conditions were examined next in order to avoid the ring-expansion of the cyclopropene to the cyclopentadiene. Conducting the reactions at −45 °C was optimal, and under these conditions, cyclopropenes **11a**−**q** were formed in generally good yields (45−89%) and in very high enantiomeric excess (95−99% ee) (Table 1). Increasing the length of the alkyl chain or the bulkiness of the alkyne substituent had virtually no effect on the enantioselectivity of the cyclopropenation reaction. Relatively low yield, however, was obtained when 2,2-dimethylbutyne was used (entry 9). Benzylic C−H insertion was not observed in the case of entries 10−12, suggesting that the cyclopropenation is a very favorable reaction. Monocyclopropenation of the diynes used in entries 13 and 14 was a viable process. Clean cyclopropenation and no C−H insertion adjacent to an electron-donating siloxy group was observed in the case of entries 15 and 16. These studies demonstrate that the cyclopropenation reaction can occur in a highly selective manner with a variety of alkyl acetylenes. In contrast to the reaction with mono-substituted alkynes, no cyclopropene product was

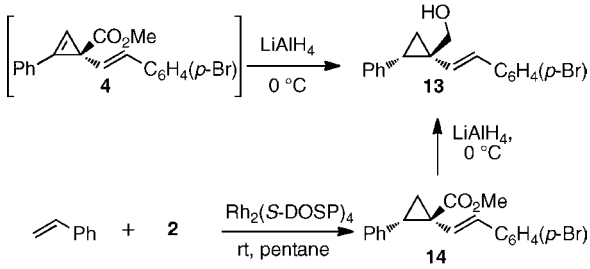
Table 2. Synthesis of Cyclopentadienes **12a**−**h**[a]



entry	R	product	yield, %
1		**12a**	61
2		**12b**	62
3		**12c**	74
4		**12d**	83
5		**12e**	82
6		**12f**	75
7		**12g**	64
8		**12h**	71

[a] Reactions were performed by addition of 1.0 mmol of **2** in 10 mL of 2,2-dimethylbutane, 0.5 mmol alkyne, and 0.01 mmol catalyst. [b] When the reaction was conducted using dirhodium(II) tetraoctanoate as catalyst, the yield of **12a** was 59%.

Scheme 4. Proof of Absolute Configuration of **4**



generated from reactions with disubstituted alkynes, such as 1-phenyl-1-propyne and diphenylacetylene.

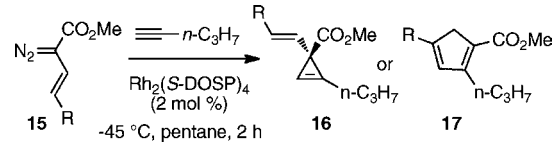
As cyclopentadienes represent an interesting class of reagents in organic synthesis, efforts were made to optimize their formation. Upon heating the reaction mixture to reflux, using 2,2-dimethylbutane (DMB) as solvent, a range of cyclopentadienes (**12a**−**h**) was formed in moderate to good yields (61−83% yield) (Table 2).

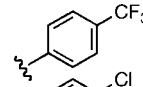
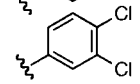
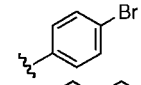
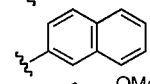
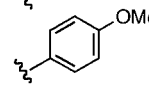
The absolute configuration of the cyclopropenes was assigned in the following manner (Scheme 4). The *in situ* formed cyclopropene **4** from the reaction of **2** and **3** was trapped by addition of $LiAlH_4$ to afford alcohol **13** as a single diastereomer. Chiral HPLC analysis of **13** (92% ee) confirmed that it was the (1*S*, 2*S*)-enantiomer based on comparison of the retention time with **13** obtained from the reduction of cyclopropane **14** derived from **2** and styrene.[13] The same absolute configuration was observed with the silyl-substituted cyclopropene **11q**, which was determined by X-ray crystallography.[14] The absolute configurations of the other cyclopropenes are tentatively assigned by analogy.

(13) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

(14) The crystal structure of **11q** and **17d** have been deposited at the Cambridge Crystallographic Data Centre, and the deposition numbers CCDC 765701 and 765700 have been allocated.

Table 3. Rh_2(*S*-DOSP)$_4$-Catalyzed Reactions of **15**[a]



entry	R =	product	yield, %	ee, %
1		**16a**	88	98
2		**16b**	79	96
3		**16c**	86	97
4		**17a**	87	--
5		**17b**	78	--

[a] Reactions were performed by addition of 1.0 mmol of diazo compound in 10 mL of pentane, 0.5 mmol alkyne and 0.01 mmol catalyst.

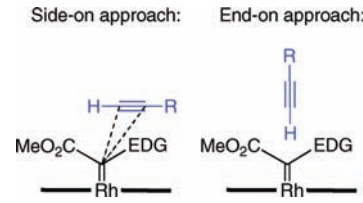


Figure 1. Extreme orientations of incoming substrate in cyclopropenation chemistry.

Other arylvinyldiazoacetates (**15**) were also tested in the cyclopropenation reaction (Table 3). In the case of relatively electron-deficient arylvinyldiazoacetates (entries 1−3), cyclopropenes **16a**−**c** were obtained in good yields (79−88%) and high enantiomeric excess (96−98% ee). In contrast, the reaction of the more electron-rich arylvinyldiazoacetates (entries 4 and 5) resulted in ring-expansion and consequent formation of cyclopentadienes **17a** and **17b** in 87% and 78% yields, respectively. The structure of **17a** was confirmed by X-ray crystallography.[14]

The high enantioselectivity observed in the cyclopropenation reactions suggests that the alkyne approaches the vinylcarbenoid intermediate in a highly organized manner. There are two extreme orientations proposed for the approach of the alkyne during the cyclopropenantion event (Figure 1).[11] The first has the alkyne approaching side-on,[13] while the second has the alkyne approaching end-on to the rhodium carbenoid.[15] The observation that no cyclopropenantion occurs with disubstituted alkynes would be evidence to support the end-on approach, as such an approach would be highly unfavorable for disubstituted alkynes since the second substituent will clash with the rhodium catalyst structure.[11] However, an end-on approach does not give an obvious explanation of why Rh_2(*S*-DOSP)$_4$ gives such high

(15) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902–15911.

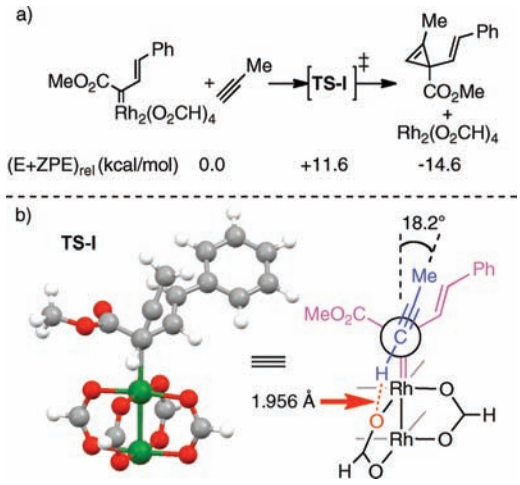


Figure 2. (a) Model reaction system, (b) transition state **TS-I** for cyclopropenation reaction.

asymmetric induction. The chiral influence of Rh_2(*S*-DOSP)$_4$ has been proposed to be due to steric influence located, not directly in front of the rhodium−carbon bond, but slightly to the side of the carbenoid.[13,15] An end-on approach is unlikely to be influenced by steric groups located to the side of the carbenoid.

Density Functional calculations were conducted in order to obtain a better understanding of the mechanism of the cyclopropenation reaction. The study was conducted using the B3LYP functional[16] in the reaction between methyl styryldiazoacetate (**6**) and propyne, catalyzed by dirhodium tetrakisformate, as a model reaction system (Figure 2a). Only the reaction step involving the rhodium carbenoid complex and propyne was considered, as the pathway leading to the rhodium carbenoid complex has been described in detail in previous works.[15,17] The cyclopropenation step displayed a potential energy activation barrier of +11.6 kcal/mol, and was exothermic by −14.6 kcal/mol. These observations suggest that a much later transition state occurs in cyclopropenation chemistry in comparison with cyclopropanation reactions of alkenes.[15,17a] Starting from either an end-on or side-on trajectory, the alkyne ultimately obtained approximately the same orientation in all the transition state optimizations. The favored transition structure (**TS-I**) is shown in Figure 2b (see Supporting Information for more details). A most striking feature of this transition state is the close proximity and directionality of the terminal alkyne hydrogen to a carboxylate ligand (1.956 Å), which indicates a hydrogen bonding interaction.[18] The alkyne is furthermore tilted 18.2° from the ideal end-on approach. These observations imply that a disubstituted alkyne could not have a suitable orientation to undergo the cyclopropenation reaction.

The tilted substrate orientation observed in **TS-I** is of critical importance, as it ensures that the chiral influence of Rh_2(*S*-DOSP)$_4$ would be involved in the asymmetric induction. As this complex is considered to adopt a D_2-symmetric conformation, the chiral carbenoid complex can be represented with blocking groups from the catalyst occupying the front left-hand and the back right-hand quadrants (Figure 3).[13,15] The substrate approaches in a tilted orientation so that attack occurs to the front face (*Re*-face) of the carbenoid preferentially. Approach to the *Si*-face is disfavored by the blocking group in the back, as it is on the side of the vinyl group. In the transition state, the terminal alkyne carbon is involved in C−C bond formation with the carbenoid carbon, while positive charge buildup occurs at the internal sp-carbon. The second C−C bond forms with inversion at the carbenoid center, consistent with previous observations in cyclopropanation and C−H functionalization chemistry.[15,17] This model successfully predicts the sense of asymmetric induction in these reactions.

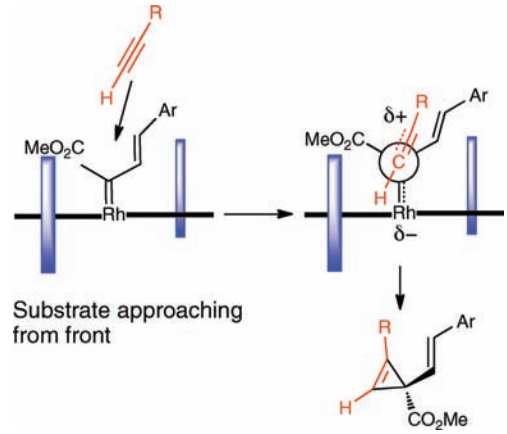
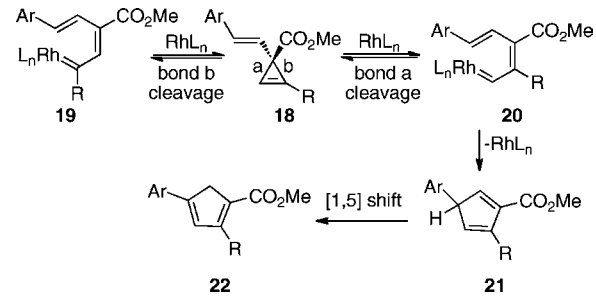


Figure 3. Predictive model for asymmetric induction in cyclopropenation chemistry with Rh_2(*S*-DOSP)$_4$.

Scheme 5. Mechanistic Hypothesis for formation of **22**



The proposed mechanism for the formation of the cyclopentadiene product is based on previous studies by Padwa and coworkers.[3b] The rhodium catalyzed ring-opening of unsymmetrically substituted vinylcyclopropene **18** can potentially lead to two regioisomeric rhodium-carbenoids **19** and **20**, depending on which bond is cleaved (Scheme 5).[3b,19] Literature precedence indicates that further reaction occurs preferentially from the least substituted carbenoid **20**.[20] This may be due to preferential cleavage of bond **a** to form **20**, or rapid equilibration between

(16) See Supporting Information for details and references. The geometry optimizations and frequency calculations were carried out using the B3LYP functional as implemented in Gaussian'09. The Stuttgart 1997 relativistic small-core ECP and corresponding basis set augmented with a 4f-function was used for Rh (abbreviated [Rh-RSC+4f]) and 6-31G* was used for C, H and O. Single point energies were furthermore calculated at the B3LYP/6-311+G(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level of theory. The discussion is based on these single point energies corrected with zero-point energies from the B3LYP/6-31G*[Rh-RSC+4f] level calculations.

(17) (a) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555–6563. (b) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181–7192.

(18) (a) For an example of hydrogen bonding in rhodium carbenoid chemistry between hydroxyl ylides and the carboxylate ligand, see: Liang, Y.; Zhou, H.; Yu, Z.-X. *J. Am. Chem. Soc.* **2009**, *131*, 17783−17785. (b) General reference for hydrogen bonding characteristics: Jeffrey, G. A. *An Introduction to Hydrogen-Bonding*; Oxford University Press, Inc: New York, 1997.

(19) Muller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V. *Helv. Chim. Acta* **1990**, *73*, 1233.

the isomeric vinylcarbenoids, with cyclopentadiene formation occurring from **20**. The initially formed cyclopentadiene **21** would then need to undergo a [1,5]-sigmatropic rearrangement to form the observed product **22**.

Conclusions

In summary, arylvinyldiazoacetates were found to be effective systems for highly enantioselective Rh_2(*S*-DOSP)$_4$ -catalyzed cyclopropenation reactions with terminal alkynes. A new class of chiral vinylcyclopropenes with quaternary carbons is now readily accessible. Under forcing conditions, the vinylcyclopropenes undergo a rhodium(II)-catalyzed ring expansion to stable cyclopentadienes. Density functional calculations have demonstrated that the exact transition state for the cyclopropenation event involves a tilted end-on approach that also displays a favorable hydrogen-bonding interaction with a carboxylate ligand on the catalyst. These observations provide valuable insights for future catalyst design and expansion of this methodology to more elaborate systems.

Experimental Section

Representative Example for Cyclopropenation of Alkynes. A mixture of 1-pentyne (0.5 mmol) and Rh_2(*S*-DOSP)$_4$ (0.01 mmol) was dissolved in 1 mL of pentane and stirred at −45 °C under an atmosphere of argon. Methyl phenylvinyldiazoacetate **6** (1.0 mmol) in 10 mL of pentane was then added to former solution via syringe pump over 2 h. After addition, the mixture was stirred for additional 20 min, then concentrated *in vacuo*. The residue was purified on silica using 15:1 hexane/diethylether as solvent system to give cyclopropene **11a** in 81% yield (99 mg) as yellow oil. 99% ee (determined by HPLC: (R,R)-Whelk, 5% *i*-PrOH in hexanes t_R = 8.37 (major) t_R = 9.82 (minor)). IR (neat) 1716, 1245, 743 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.15−7.38 (m, 6H), 6.33 (app t, 1H, J = 1.5 Hz), 6.04 (d, 1H, J = 15.9 Hz), 3.72 (s,1H), 2.49 (td, 2H, J = 7.5, 1.5 Hz), 1.62 (s, 2H, J = 7.5 Hz), 0.98 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz) δ 176.2 (C═O), 137.7 (C), 131.7 (CH), 128.7 (CH), 127.9 (CH), 127.1 (CH), 126.3 (CH), 116.7 (C), 93.3 (CH), 52.2 (CH_3), 30.6 (C), 25.7 (CH_2), 20.6 (CH_2), 13.9 (CH_3). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.13014.

Representative Example for Synthesis of Cyclopentadienes. To a two-neck, round-bottom flask equipped with condenser was added 1-pentyne (0.5 mmol), Rh_2(*S*-DOSP)$_4$ (0.01 mmol), and 1 mL of 2,2-dimethylbutane (DMB). The solution was stirred under an atmosphere of argon then heated to reflux. Methyl phenylvinyldiazoacetate **6** (1.0 mmol) in 10 mL of DMB was then added to former solution via syringe pump over 2 h. After addition, the mixture was allowed to warm to room temperature. After stirring for additional 20 min, the crude reaction mixture was concentrated *in vacuo*. The residue was purified on silica using 15:1 hexane/diethyl ether as solvent system to give cyclopentadiene **12a** in 61% yield (75 mg) as yellow oil. IR (neat) 1696, 1205, 717 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.57 (d, 2H, J = 7.2 Hz), 7.25−7.37 (m, 3H), 6.84 (s, 1H), 3.78 (s,1H), 3.74 (d, 2H, J = 1.2 Hz), 2.84 (t, 2H, 7.6 Hz), 1.64 (s, 2H, J = 7.6 Hz), 0.98 (t, 3H, J = 7.6 Hz; ^{13}C NMR (100 Hz) δ 165.5 (C═O), 161.0 (C), 150.9 (C), 135.1 (C), 130.7 (CH), 128.9 (CH), 128.3 (CH), 127.4 (C), 125.8 (CH), 51.0 (CH_3), 42.3 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 22.9 (CH_2), 14.2 (CH_3). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.13004.

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Supporting Information Available: Complete Gaussian'09 reference. Experimental details and characterization data are available for all compounds. Cartesian coordinates and a summary of calculated parameters are available for theoretical structures reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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