The Development of an Asymmetric Nicholas Reaction Using Chiral Phosphoramidite Ligands

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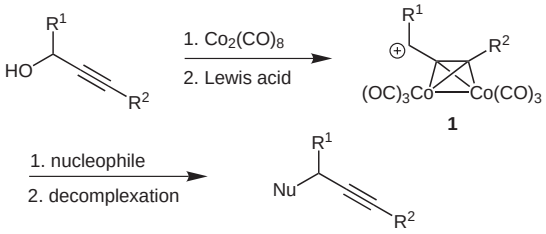
Abstract: An asymmetric version of the Nicholas reaction involving the use of chiral phosphoramidite ligands has been developed. Treatment of a cobalt carbonyl complexed propargylic alcohol with two equivalents of the chiral ligand, followed by reaction with a silyl enol ether in the presence of a Lewis acid, afforded, after decomplexation, the desired product in up to 74% ee for the carbon–carbon bond forming step.

Key words: asymmetric synthesis, organometallic reagents, phosphorus, nucleophiles, ligands



Scheme 1 The Nicholas reaction

The Nicholas reaction (Scheme 1) is a versatile transformation, involving the reaction of a cobalt carbonyl stabilized propargylic cation **1** with different nucleophiles.[1] The scope of nucleophiles that can be applied in the Nicholas reaction is wide, including alcohols, amines, thiols, fluoride, hydride, phosphines, as well as various types of carbon nucleophiles in the form of enol ethers, electron-rich aromatics, allyl silanes, allyl stannanes, and trialkyl aluminum reagents.[1a] Complexation of the precursor propargylic alcohols or ethers with dicobalt octacarbonyl proceeds smoothly at room temperature, and the dark red complex formed is subsequently treated with a Lewis acid to generate the cation prior to addition of the nucleophile. Decomplexation is generally effected oxidatively, using cerium ammonium nitrate or iodine. Recent developments in this area include a tandem Nicholas–Pauson–Khand sequence,[2] the use of montmorillonite K-10 to generate the stabilized cation,[3] a solid-phase version of the reaction,[4] as well as the synthesis of natural product hybrids,[5] and bioactive polyether structures.[6] Recently, related reactions involving the use of rhenium[7] or ruthenium[8] catalysts have been developed, and successful enantioselective versions of these reaction have in some cases been carried out,[9] although their full scope has not yet been investigated. In this communication we report the successful development of an asymmetric version of the Nicholas reaction using chiral phosphoramidites as ligands to cobalt.

Asymmetric versions of the Nicholas reaction have in general involved the use of chiral nucleophiles[10] or chiral substrates.[11] Chirality transfer has also been performed.[12] However, to our knowledge the use of racemic propargylic alcohols in conjunction with chiral ligands coordinated to cobalt have not been reported for the Nicholas reaction, and we thus embarked on an investigation into this matter. Our initial screening of chiral phosphine ligands in the Nicholas reaction showed that the propargylic cobalt complexes formed suffered from low reactivity, in agreement with earlier reports by Nicholas[13] and Mayr.[14] Phosphites showed more promise in activating the complex for nucleophilic attack.[12b] Although chiral phosphite ligands have been used in asymmetric reactions,[15] we instead opted for the structurally similar class of phosphoramidite ligands that have been extensively employed lately.

Chiral phosphoramidites are versatile ligands employed in a number of asymmetric transformations,[16–18] having the additional advantage that such compounds are facile to prepare in a parallel format.[19] Gimbert and colleagues have applied phosphoramidite ligands in asymmetric Pauson–Khand reactions with promising enantioselectivities,[20] while Buono and co-workers have reported an asymmetric Co(I)-catalyzed [6+2]-cycloaddition using a phosphoramidite ligand, also with good results.[21] To our knowledge, these are the only examples of the application of phosphoramidite ligands in cobalt-catalyzed organic synthesis. We thus decided to prepare a library of chiral phosphoramidite ligands for an initial screening in an asymmetric Nicholas reaction to expand the scope of these ligands in terms of organocobalt reactions.

For the library of phosphoramidites, (*S*)-BINOL [(*S*)-(–)-1,1′-bi-2-naphthol] was used as the diol component in all cases, with a focus on varying the amine moiety. Fourteen different amines were selected and the corresponding phosphoramidites were prepared via the chiral chlorophosphite of (*S*)-BINOL, following the procedure reported by Feringa, de Vries and co-workers for ligand synthesis in a parallel format (Figure 1).[22] Twelve of these phosphoramidite ligands have been reported earlier,[23] while **2b** and **2c** are new.[24] The selection of precursor

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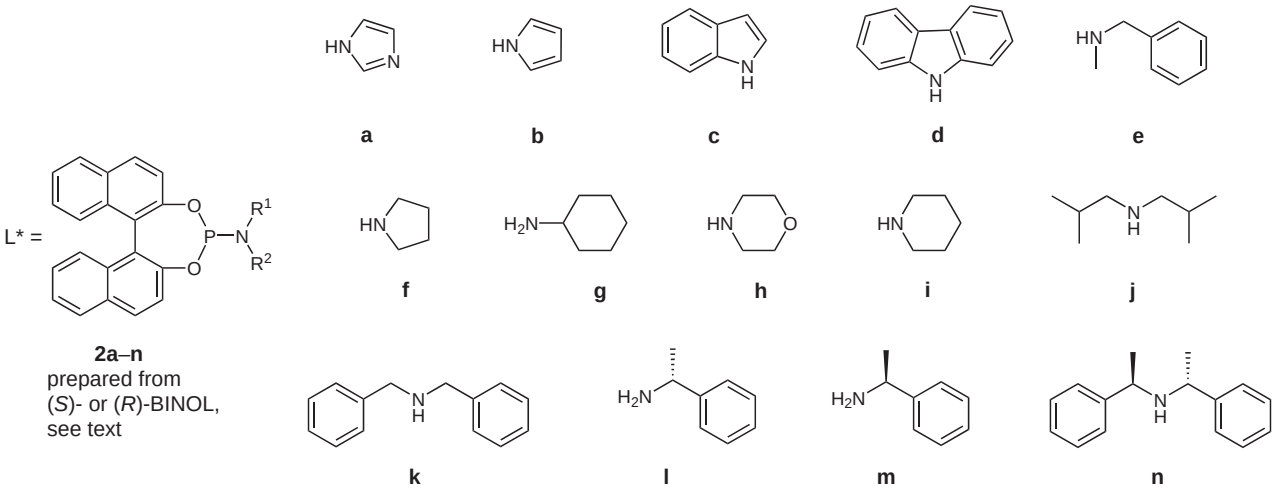
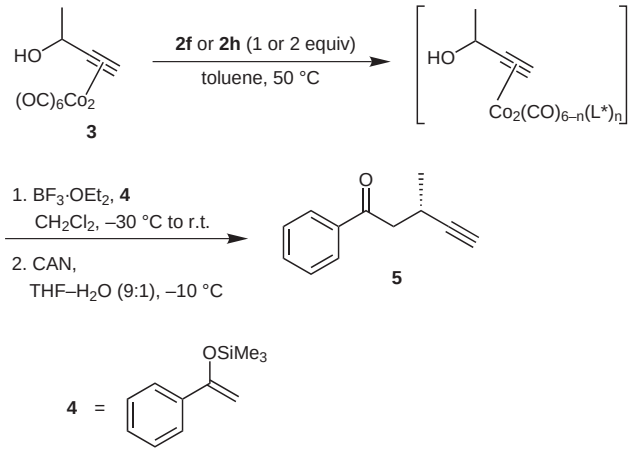


Figure 1 Chiral phosphoramidites used in the asymmetric Nicholas reaction

amines comprised both aliphatic and aromatic structures, as well as three chiral amines.

Before the full screening of the ligands in the Nicholas reaction was approached, a preliminary investigation into the optimal number of ligands on the complex was carried out, limiting this initial study to two ligands, i.e. the pyrrolidine-substituted ligand **2f** as well as MorfPhos (**2h**), both prepared from (*R*)-BINOL [(*R*)-(+)-1,1′-bi-2-naphthol] in this case. A commercially available alkynol, 1-butyn-3-ol was converted into the corresponding dicobalt hexacarbonyl complex **3**[25] (Scheme 2). Ligand exchange was effected by heating complex **3** with one or two equivalents of ligands **2f** or **2h** in toluene at 50 °C under an argon atmosphere.[26] The intermediate ligand-substituted complexes were not isolated, but used directly in the Nicholas reaction. To each reaction flask, at –30 °C, were added two equivalents of 1-phenyl-1-(trimethylsilyloxy)ethylene (**4**) together with 1.5 equivalents of boron trifluoride etherate.[27] The reaction was allowed to warm to room temperature overnight, the solvent was evaporated and the residue was treated with a solution of cerium ammonium nitrate in THF–H_2O (9:1) at –10 °C to liberate the substituted alkyne **5**. The enantioselectivity of the reaction was subsequently determined by chiral HPLC analysis (see Table 1). The enantiomeric excesses in these initial reactions were modest but promising for a first attempt, with two equivalents of ligand (entries 2 and 4) giving better results than the corresponding reactions with one equivalent (entries 1 and 3). One limitation, however, was that the enantiomers of **5** were not easily separable by HPLC, and we thus decided to search for another target molecule for a more reliable test reaction.

Diketone **7** (Scheme 3), prepared in racemic form in a related project,[4b] showed good separation of the two enantiomers by chiral HPLC and was thus selected as a target for the screening of ligands in the asymmetric Nicholas reaction. Propargylic alcohol **6**, was synthesized via a microwave-assisted Sonogashira reaction from *p*-iodoacetophenone and 3-hydroxy-1-octyne.[30]

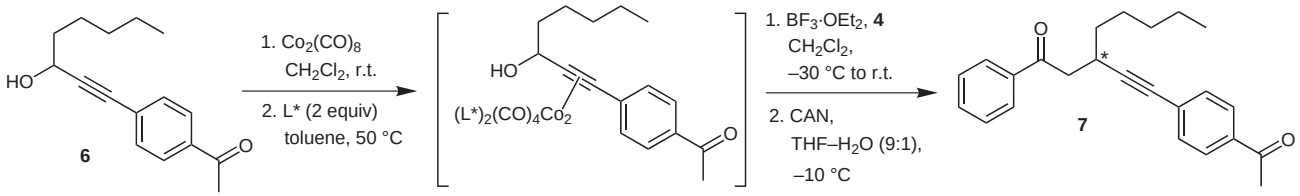


Scheme 2 Optimization of the ligand-to-substrate ratio in the asymmetric Nicholas reaction with **3**; in this case, ligands **2f** and **2h** were prepared from (*R*)-BINOL

Table 1 Results from Initial Nicholas Reactions with **3** (Scheme 2)

Entry	Ligand[a]	Amount (equiv)[b]	Yield (%) of **5**[c]	ee[d,e]
1	**2f**	1	26	16 (*S*)
2	**2f**	2	33	24 (*S*)
3	**2h**	1	12	20 (*S*)
4	**2h**	2	10	26 (*S*)

[a] Prepared from (*R*)-BINOL.
[b] Relative to complex **3**.
[c] Overall yield of the isolated product calculated over three steps, from complex **3**.
[d] Determined by HPLC analysis using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH, 9:1).
[e] Absolute configuration was determined by oxidative cleavage of the alkyne with RuO_2–oxone[28] to the corresponding carboxylic acid, and comparison with the previously reported data for the optical rotation.[29]



Scheme 3 Screening of phosphoramidite ligands in the asymmetric Nicholas reaction; see Figure 1 for ligand structures L* [prepared from (*S*)-BINOL]

Complexation with dicobalt octacarbonyl was carried out in dichloromethane at room temperature for three hours while protecting the flask from light, followed by purification via elution through a short plug of silica to afford the corresponding cobalt carbonyl complexed alkyne as a dark red oil. Formation of the phosphoramidite–cobalt carbonyl–alkyne complexes was effected in a parallel format in a Radleys carousel[31] following the procedure described earlier for the test reaction,[26] and the Nicholas reaction was carried out in the same manner as reported earlier.[27] The enantioselectivity was then measured by HPLC both before the purification and on the compound isolated after flash chromatography (Table 2).

The use of phosphoramidite ligands prepared from aromatic amines, i.e. **2a**, **2b**, **2c** and **2d**, in general gave both low yields and discouraging enantioselectivities. Moyano and co-workers have shown that aromatic substituents on a phosphoramidite ligand can act as internal nucleophiles when coordinated to a cationic propargylic cobalt alkyne,[32] and this could be one explanation for the poor results in these cases as well as the fact that the opposite enantiomer was formed when using ligands **2b** and **2d**. Ligands formed from secondary aliphatic amines showed more promise. Ligand **2e**, containing a *N*-methylbenzylamine functionality, produced **8** in 40% ee, while even better results were obtained with ligands incorporating a cyclic secondary amine. MorfPhos (**2h**) and PipPhos (**2i**) gave 60% and 64% ee values, respectively, while 70% ee was obtained for the pyrrolidine-substituted ligand **2f**. Phosphoramidite **2l**, incorporating a chiral amine, afforded the product with a respectable ee of 30%, while the diastereomeric ligand **2m** produced the same enantiomer of the product but with a lower ee, indicating a mismatched situation. This also suggests that the BINOL moiety determines the stereochemical outcome of the reaction, although the actual structure of the amine (i.e. primary/secondary, aliphatic/aromatic) is of importance as seen from the earlier mentioned results. Chiral ligand **2n** gave racemic product in low yield. It may be that the complex formed in this case was too sterically encumbered to undergo a Nicholas reaction in the presence of a nucleophile. Ligand **2j**, being sterically somewhat less hindered, also gave a better ee (32%), as did the dibenzylamine ligand **2k** (54%). The yields for the reactions may seem modest; however, they were calculated over four steps, indicating average yields of around 80% for each individual step for the more interesting ligands **2f**, **2h** and **2i**. Although overlapping impurities in a few instances interfered with the determination of the enantiomeric purity of the crude product, there was little difference in the enantiomeric excess measured before and after purification, indicating that a rapid screening of chiral ligands can be effected without the need of purifying the product.

Table 2 Results from the Asymmetric Nicholas Reaction with Alkynol **6** (Scheme 3)

Entry	Ligand[a]	ee, crude product (%)[b]	Yield (%) of **7**[c]	ee (%)[b]
1	**2a**	0	30	0
2	**2b**	n.d.[d]	9	6[e]
3	**2c**	n.d.[d]	6	16
4	**2d**	8[e]	11	6[e]
5	**2e**	38	33	40
6	**2f**	74	35	70
7	**2g**	18	35	16
8	**2h**	62	44	60
9	**2i**	68	47	64
10	**2j**	36	47	32
11	**2k**	52	14	54
12	**2l**	n.d.[d]	35	30
13	**2m**	10	8	8
14	**2n**	n.d.[d]	7	0

[a] Prepared from (*S*)-BINOL.
[b] Determined by HPLC analysis using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH, 9:1).
[c] Overall yield of the isolated product calculated from propargylic alcohol **6**.
[d] It was not possible to determine the ee of the crude product due to overlapping impurities.
[e] Opposite enantiomer in excess.

To expand the scope of the reaction, a preliminary investigation involving two more carbon nucleophiles, as well as an alternative substrate, was carried out (Figure 2). 4-(3,5-Dimethylphenyl)-3-butyn-2-ol (**8**)[30] was subjected to the same reaction conditions as displayed in Scheme 2, with the exception that three different nucleophiles were used in conjunction with the pyrrolidine-substituted phosphoramidite ligand **2f**, i.e. the best ligand in the earlier experiments.

Treatment of the intermediate ligand-substituted cobalt–alkyne complex with 3-methoxyanisole afforded the de-

sired product **9** in good yield but with a disappointing ee of 12% (Table 3, entry 1). *N*-Methylindole likewise gave a rather low enantioselectivity of **10** (entry 2), albeit with an excellent overall yield. The reaction of 1-phenyl-1-(trimethylsilyloxy)ethylene, i.e. nucleophile **4** from Scheme 2, was more promising in terms of asymmetric induction, affording product **11** in 66% ee with ligand **2f** (entry 3).

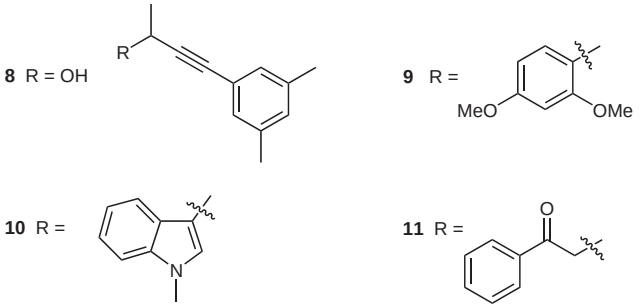


Figure 2 Nucleophiles used in conjunction with alkynol **8**

Table 3 Reaction of Phosphoramidite Ligands **2f** and **2h** with Various Nucleophiles

Entry	Ligand[a]	Nucleophile	Prod	Yield (%)	ee (%)[b]
1	**2f**	3-methoxyanisole	**9**	74	12
2	**2f**	*N*-methylindole	**10**	90	22
3	**2f**	**4**	**11**	30	66
4	**2h**	**4**	**11**	17	74

[a] Prepared from (*S*)-BINOL.
[b] Determined by HPLC analysis using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH, 9:1).

This reaction was also carried out with **2h**, i.e. the morpholine-substituted phosphoramidite ligand, which in this case performed even better than its pyrrolidine counterpart, with an enantiomeric excess of 74% for the product (entry 4). Although the overall yields in the reactions involving the more sensitive nucleophile **4** need to be improved, these results show that the methodology is applicable to other substrates as well.

In summary, we have shown that phosphoramidite ligands are applicable in the asymmetric Nicholas reaction with carbon nucleophiles, affording up to 74% ee using a silyl enol ether nucleophile. Further studies involving several substrates and also including heteroatom nucleophiles are currently in progress to investigate the scope of the reaction and to further improve the enantioselectivity and yields.

Acknowledgment

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(24) **General Procedure for the Parallel Synthesis of the Ligands**:[21] The amine (0.25 mmol) was added to a carousel tube, followed by Et_3N (0.25 mmol). The tube was sealed, flushed with argon and cooled to –40 °C. A 0.25 M stock solution of BINOL-chlorophosphite (1 mL) in toluene was added, and the reaction was left to warm overnight. The reaction mixture was rapidly filtered through a small plug of silica gel into a new sealed and degassed carousel tube. The filtrate was washed with toluene (1 mL), and the combined toluene solutions of the ligand were used directly in the next step.

Spectral Data for Crude 2b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–8.10 (m, 4 H), 7.20–7.60 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 144.9, 132.0, 131.6, 131.5, 128.7, 128.6, 127.3, 127.2, 127.0 (*J* = 2.3 Hz), 126.2, 126.1, 121.0, 120.2 (*J* = 38 Hz). IR: 1298, 1224, 966, 929, 881, 816, 752 cm^{-1}.

Spectral Data for Crude 2c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–8.00 (m, 4 H), 7.25–7.60 (m, 14 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 147.1, 132.9, 132.6, 131.8, 131.4, 130.6, 130.0, 128.6 (d, *J* = 7.6 Hz), 127.1 (d, *J* = 9.9 Hz), 126.5, 126.4, 125.4, 125.1, 124.5, 123.2, 122.0, 121.8. IR: 1225, 1198, 884, 820 cm^{-1}.

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(26) **General Procedure for the Formation of the Intermediate Cobalt Complexes**: The propargylic alcohol (1-butyn-3-ol, **6** or **8**) was dissolved in CH_2Cl_2 in a two-necked flask under argon. An equimolar amount of dicobalt octacarbonyl, dissolved in CH_2Cl_2, was added. The reaction was protected from light by wrapping the flask in foil, and the solution was stirred at r.t. for 3 h. The mixture was filtered through a short plug of silica, eluting with CH_2Cl_2, and concentrated, affording the complex as a dark red oil. The ligand (0.25 mmol) was added to a Radleys carousel tube and dissolved in toluene (1 mL). The tube was sealed and flushed with argon. A 0.125 M stock solution of the alkyne–cobalt complex (1 mL) in toluene was added to the tube. The reaction mixture was heated at 50 °C overnight. The solvent was removed in vacuo, and the crude phosphoramidite–cobalt–alkyne complex thus formed was used directly in the Nicholas reaction in the same reaction tube.

(27) (a) **General Procedure for the Asymmetric Nicholas Reaction**: The phosphoromidite–cobalt–alkyne complex (0.25 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to –30 °C. $BF_3{\cdot}OEt_2$ (47.5 μL, 0.375 mmol,) was added, followed by the dropwise addition of the nucleophile (0.5 mmol). After 16 h, the reaction was quenched with Et_3N (69.7 μL, 0.5 mmol), and the solvent was removed in vacuo. Decomplexation was effected by dissolving the residue in THF–H_2O (9:1), cooling to –10 °C, followed by the portionwise addition of a 0.18 M solution of cerium ammonium nitrate in THF–H_2O (9:1) until the dark red solution turned orange-yellow (the amount of CAN solution used corresponded to approximately 5 equiv in most cases, and up to 10 equiv in a few cases). The reaction mixture was diluted with brine (1 mL) and extracted with Et_2O (3 × 2 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography, eluting with 5–10% EtOAc in PE. The enantioselectivity was measured by HPLC on both the crude and the pure product, using a Daicel Chiralpak AD-H column (hexane–*i*-PrOH, 95:5). (b) For compound **5**, see: Asao, N.; Ohishi, T.; Sato, K.; Yamamoto, Y. *Tetrahedron* **2002**, *58*, 8195. (c) For compounds **7**, **9**, **10** and **11**, see ref. 4b.

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(30) **General Procedure for the Preparation of the Precursor Propargylic Alcohols, Exemplified by 6**: 4-Iodoacetophenone (500 mg, 2.03 mmol), $Pd(PPh_3)_4$ (23.5 mg, 0.020 mmol) and CuI (7.7 mg, 0.040 mmol) were added to a 5-mL microwave reaction tube flushed with argon. Freshly distilled Et_3N (2 mL) and anhyd DMF (1 mL) were added, followed by 1-octyn-3-ol (355 μL, 2.43 mmol). The reaction was heated at 100 ºC for 10 min using a Biotage Initiator microwave reactor. The reaction mixture was then filtered through a pad of Celite, diluted with Et_2O and washed with brine. Drying over $MgSO_4$ followed by rotary evaporation afforded **6** (390 mg) as an amber-yellow oil. For larger-scale reactions, the reaction was run with conventional heating at 40 ºC for 16 h. Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 4.56–4.64 (m, 1 H), 2.59 (s, 3 H), 1.74–1.84 (m, 2 H), 1.30–1.60 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 136.4, 131.9, 128.3, 127.8, 93.8, 84.1, 63.1, 37.8, 31.6, 26.7, 25.0, 22.7, 14.1. IR: 3421, 2931, 2365, 2250, 1684, 1602, 1266, 909, 733 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.53; H, 8.65. Compound **8** was prepared from 1-octyn-3-ol and 3,5-dimethyl-1-iodobenzene in the same manner. Data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (s, 2 H), 6.96 (s, 1 H), 4.72–4.80 (m, 1 H), 2.92 (s, 6 H), 1.94 (d, *J* = 5.2 Hz, 1 H), 1.55 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.00, 130.44, 129.56, 122.47, 90.63, 84.43, 58.95, 24.63, 21.29. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.65; H, 8.03.

(31) Carousel 12 Reaction Station was obtained from Radleys Discovery Technologies.

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