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Alkyne Hydroheteroarylation: Enantioselective Coupling of Indoles and Alkynes via Rh-Hydride Catalysis

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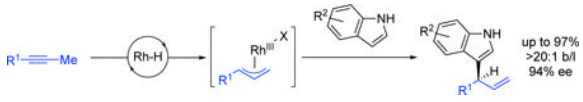
Abstract

We report an enantioselective coupling between alkynes and indoles. A Rh-hydride catalyst isomerizes alkynes to generate a metal-allyl species that can be trapped with both aromatic and heteroaromatic nucleophiles.

Graphical abstract



Aryl and heteroaryl rings can be used to increase non-bonding and electrostatic interactions between a small molecule and its macromolecule target.[1] Among the top selling therapeutics, more than half contain such aryl structures (Figure 1A).[2] Given the relevance of chirality in medicine, inventing enantioselective tools for introducing aromatic nucleophiles warrants pursuit.[3] The hydroarylation of alkynes is a modern strategy for functionalizing aryl-structures,[4] where two simple functional groups are coupled with high atom economy.[5] To date, however, this approach has been limited to generating achiral olefins (Figure 1B, Eq. a). Classic alkyne hydroarylations generate achiral vinylated-arenes *via* mechanisms that involve alkyne activation with π-acids or arene activation to access aryl-metal species [4d–n] In contrast, we imagined using metal-hydride catalysis to couple arenes with alkynes to form allylated products (Figure 1B, Eq. b).[6] In this communication, we disclose a regio-and enantioselective alkyne hydroheteroarylation using indoles.[7–9]

On the basis of previous studies, Rh-hydride catalysts can isomerize alkynes (**2**) to allenes (**6**) *via* a Rh-vinyl species (**5**) as depicted in Figure 2.[10] Subsequent allene insertion into a

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ASSOCIATED CONTENT
Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectral data for all new compounds (PDF)

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Rh–H generates a Rh-π-allyl species (**7**). Various oxygen-,[11] sulfur-,[12] and nitrogen-based[13] nucleophiles have been used to trap **7** and generate carbon-heteroatom bonds with stereocontrol. However, enantioselective C–C bond formation has thus far been only achieved with aldehydes *via* enamine catalysis.[14e] We recognized that the key challenge to achieving alkyne hydroarylation would be trapping Rh-π-allyl **7** with an arene **1** (an inherently weaker nucleophile) to generate **3**, with high enantio-and regiocontrol. However we were encouraged by Carreira's Ir-catalyzed polyene cyclization that demonstrates the use of arenes and hetereoarenes as terminating nucleophiles.[15]

To test this hypothesis, we examined the coupling of various arenes and heteroarenes **1** and 1-phenyl-l-propyne (**2a**) (Table 1). Successful trapping of the Rh-π-allyl species affords either the branched (**3**) or the linear regioisomer (**4**). Using a combination of a Rh-bisphosphine and diphenyl phosphate,[11c,14e] we observed that arenes and heteroarenes with a wide range of nucleophilicities, based on the Mayr scale (N= 1.33 to 11.63), were successful coupling partners.[16, 21] Initial studies using $[Rh(COD)C1]_2$, dppf and diphenyl phosphate showed that the structure of the nucleophile impacted which regioisomer was favored. For example, with benzofuran and 1,3-dimethoxybenzene, we observed the linear isomers as the major product, in accordance with previous studies using Brønsted acid catalysis (>20:1 *rr*. 29% and 35%, respectively).[17] In contrast, 3-ethyl-2,4-dimethyl pyrrole and indole generated the branched isomers upon addition to alkyne **2a** (>20:1 *rr*, 24% and 65%, respectively). On the basis of related studies on alkyne hydroamination, we imagine that regioselectivity can be controlled by tuning the catalyst and acid.[13a]

Indoles can be site-selectively prenylated at the *N*, 2-, 3-, 4-, or 7-position *via* enzymatic or synthetic processes.[18] Despite the diverse reactivity of indoles, we observed selective bond formation at the 3-position upon coupling of alkyne **2a** and indole to yield **3** as the only regioisomer.

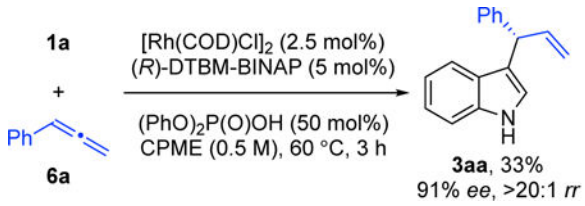
With this promising reactivity demonstrated, we focused on developing an enantioselective coupling using indoles due to the importance of these heterocycles in natural and pharmaceutical products.[19] We found that a protocol consisting of $[Rh(COD)Cl]_2$, (*R*)-Ph-BINAP (**L1**), and diphenyl phosphate gave the desired branched product (**3a**) in 5% yield and 20% *ee* (Table 2).[20] In contrast to previous studies where carboxylic acids were used,[14a–d] more acidic acids (*e.g.*, sulfonic and phosphoric acids) were necessary for reactivity. Increasing the steric bulk of the phosphine substituent improved enantioselectivity (**L2**, 28% *ee* and **L3**, 93% *ee*). The electron-rich DTBM-BINAP (**L3**) also dramatically improved the yield to 81% yield. Other biaryl bisphosphine ligands bearing the DTBM-phosphine substituents such as SEGPHOS (**L4**), GARPHOS (**L5**), or MeO-BIPHEP (**L6**) provided similar enantioselectivity but lower reactivity (18–31% yield). With ligand **L3**, we found that a number of solvents could be used but found that using cyclopentyl methyl ether (CPME) was optimal; **3a** was obtained in 92% yield and 91% *ee*, with lower (2.5 mol%) catalyst loadings.[21]

With this protocol in hand, we explored the hydroheteroarylation of alkyne **2a** with various indoles (Table 3). Efficient and selective indole-alkyne coupling occurs with a variety of indole substitution patterns. For example, a methyl group can be incorporated at the *N*-, 5-,

and 7-positions of indole to afford the corresponding allylated indoles with up to 96% yield, >20:1 *rr*, and 92% *ee* (**3ba**, **3ga**, **3oa**). In comparison, lower *ee* is observed with 2-methyl indole (**3ca**, 69% *ee*). In general, we observe lower enantioselectivity with 2-methyl indole using various aryl-substituted alkynes.[21] However, when a phenyl or tert-butyl group is incorporated at the 2-position higher *ee* is observed (**3qa** and **3ra**, 92% and 86% *ee*, respectively). Halogenated indoles were successfully coupled with high selectivities (**3da**, **3ea**, **3fa**, **3ja**, **3na**, **3pa**). Chemoselective C–C bond formation was observed in the presence of a nucleophilic phenol (**3ia**) and an electrophilic methyl ester (**3ka**). A substrate bearing a pinacol borane, a convenient functional handle was transformed smoothly (**3la**).

Next, we studied the coupling of indole **1a** with structurally diverse alkynes (Table 4). Electron-rich alkynes with alkyl or ether substitution undergo efficient and selective coupling with indole (**3ab**–**3ae**, 70–88%, >20:1 *rr*, 82–93% *ee*). Fluorinated and chlorinated alkynes act as efficient coupling partners (**3af** and **3ag**, 82–93%, >20:1 *rr*, 88–90% *ee*). In addition, electron-deficient alkynes with trifluoromethyl substitution undergo hydroarylation with indole to provide **3ai** in 97% yield and 92% *ee*. Chemoselective functionalization occurs even in the presence of electrophilic ethyl ester (**3ah**). Aromatic and heteroaromatic alkynes (3-thiophene and 1-naphthalene) also undergo hydroarylation (**3aj** and **3ak**). We found that an aromatic or heteroaromatic group on the alkyne is critical for reactivity. For example, an alkyl-substituted alkyne, such as 2-octyne, proved to be unreactive under these conditions (**3al**).

To support the intermediacy of an allene, we replaced alkyne **2a** with phenylallene **6a** (Eq. 1).[21] Under standard reaction conditions, the desired coupling product **3aa** was obtained with similar enantio-and regioselectivity, although in lower yield (33% yield, 91% *ee*, and >20:1 *rr*). This result supports the possibility of an allene intermediate. But the diminished yields suggest that high concentrations of allene may be detrimental due to competing decomposition and thus, *in situ* generation results in better efficiency.[11c, 13a]



(1)

We have demonstrated a regio-and enantioselective way to hydrofunctionalize alkynes using indoles. The use of Rh-hydride catalysis to isomerize alkynes has enabled access to a complementary hydroheteroarylation motif. Moreover, our study demonstrates the potential of generating C–C bonds under mild conditions using both aromatic and heteroaromatic motifs. Given these promising results, our future studies will focus on enantio-and regioselective coupling using other classes of aromatic nucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(20). Absolute configuration was determined by comparison of optical rotation, see SI.

(21). See SI for further experimental details, including other sub-strates evaluated, solvent evaluation, and use of a deuterated alkyne.

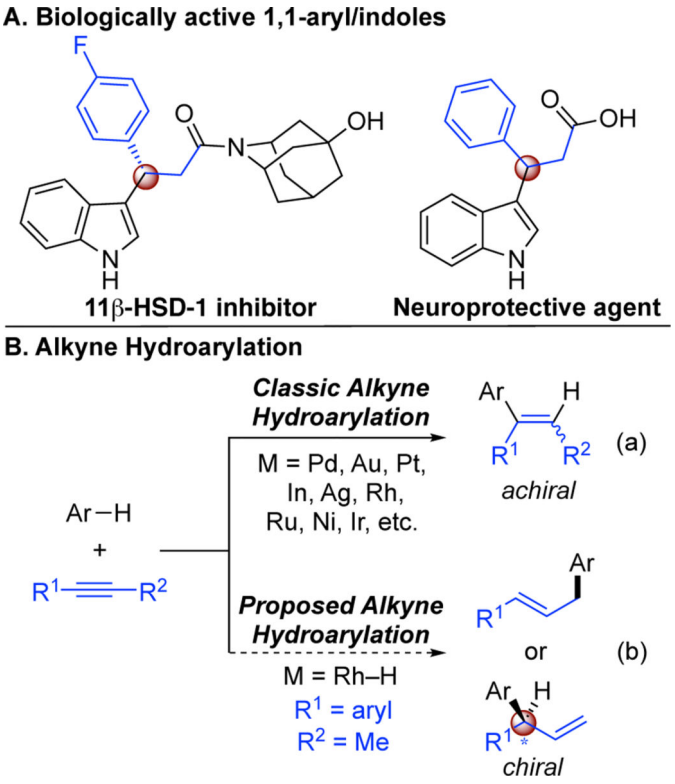


Figure 1.
Inspiration for asymmetric alkyne hydroarylation.

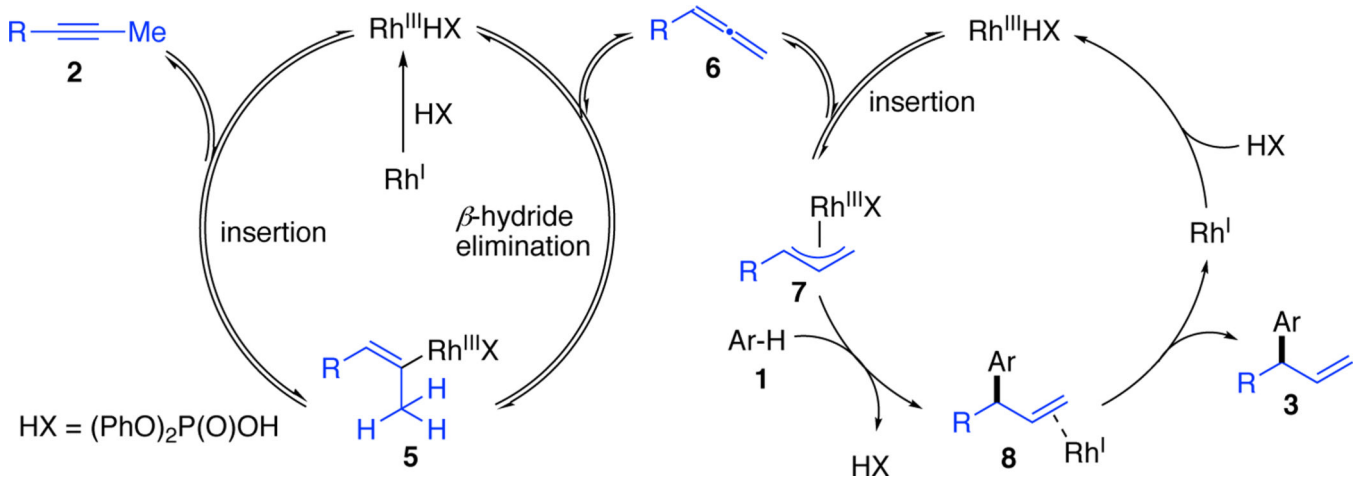
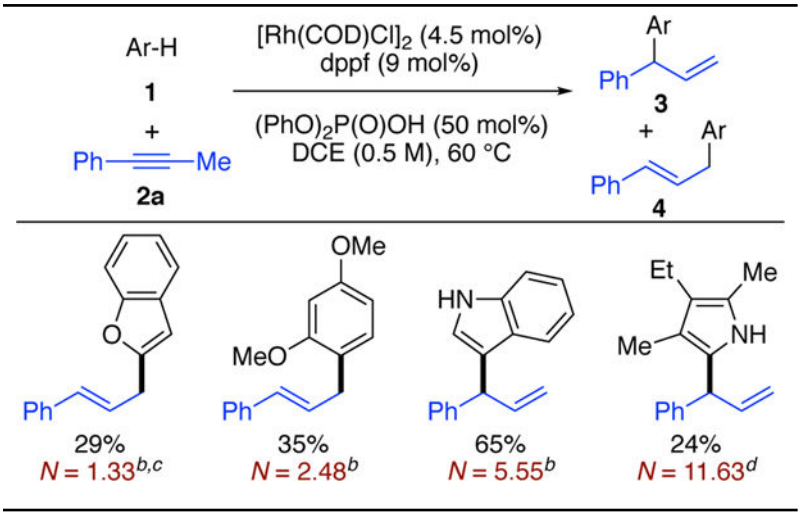


Figure 2.
Proposed Rh-hydride catalyzed alkyne hydroarylation.

Table 1.

Alkyne Hydroarylation using Arenes with a Range of Nucleophilicities[a]



[a]**1** (0.1 mmol), **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (4.5 mol%), dppf (9.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), DCE (0.2 mL), 60 °C,

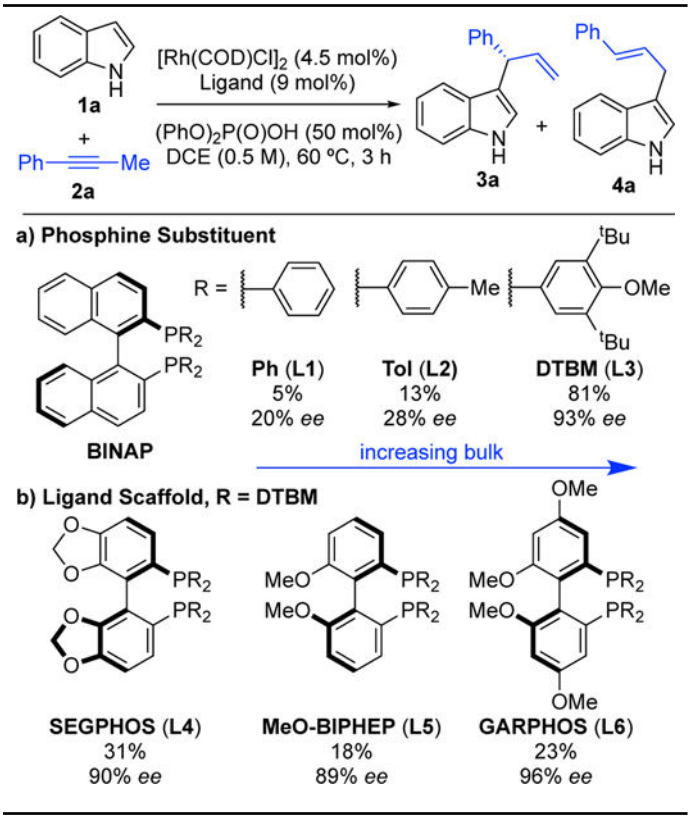
[b]Nuclcophilicity in DCM.

[c]Nucleophilicity of furan.

[d]Nucleophilicity in MeCN.

Table 2.

Ligand Effects on Alkyne-Indole Coupling[a–c]



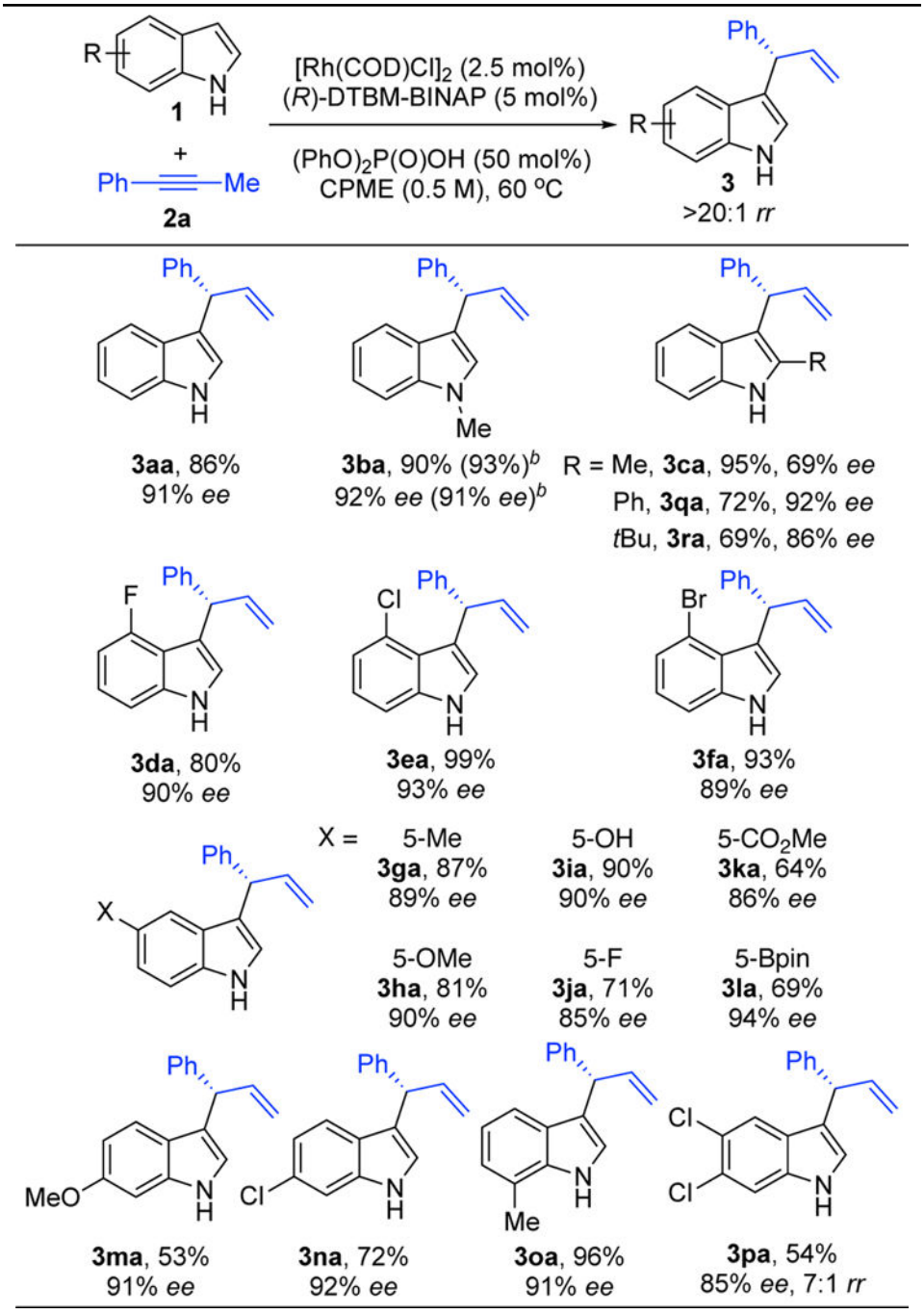
[a] **1a** (0.1 mmol). **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (4.5 mol%), ligand (9.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), DCE (0.2 mL), 60 °C, 3 hours.

[b] Yields determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as internal standard.

[c] Enantioselectivities determined by chiral SFC.

Table 3.

Alkyne Hydroheteroarylation with Various Indoles[a]

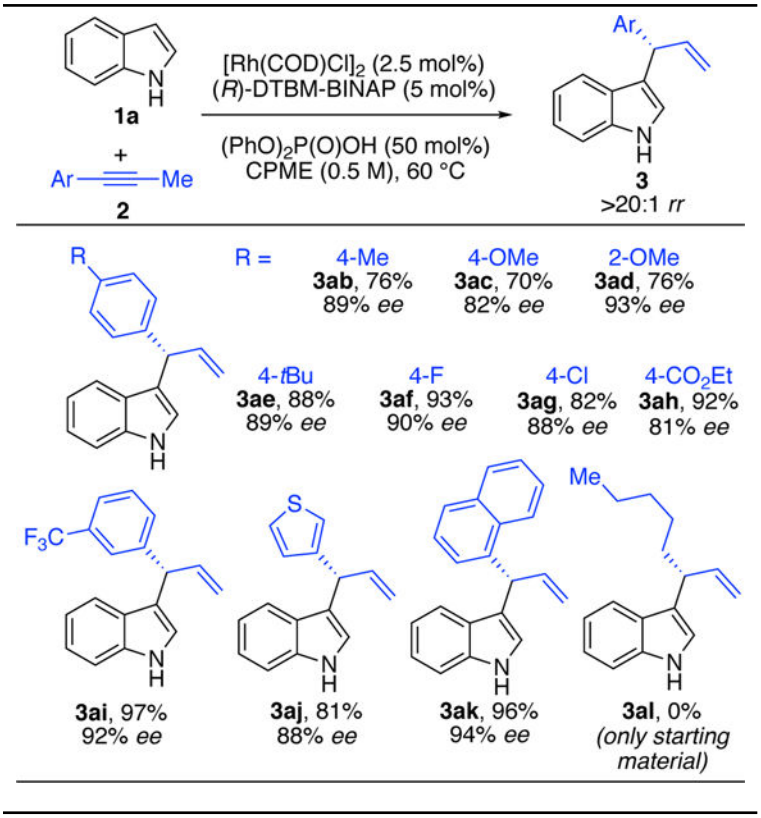


[a] **1** (0.1 mmol), **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), CPME (0.2 mL), 60 °C. Isolated yields. **rr's** (**3**:**4**) determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivities determined by chiral SFC.

[b] Values in parentheses are for the transformation performed on a 1.0 mmol scale.

Table 4.

Hydroheteroarylation of Various Alkynes with Indole[a]



[a] **1a** (0.1 mmol), **2** (0.12 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), CPME (0.2 mL), 60 °C. Isolated yields. *rr*'s (**3:4**) determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivities determined by chiral SFC.