

Literature Report



Development and Applications of Palladium(II)-Catalyzed Atroposelective C-H Alkynylation

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Liao, G.; Yao, Q.-J.; Shi, B.-F. *et al.*
Angew. Chem. Int. Ed. **2018**, *57*, 3661-3665.

CV of Bing-Feng Shi



- 1997-2001 B.Sc., Nankai University
- 2001-2006 Ph.D., Shanghai Institute of Organic Chemistry
- 2006-2007 Post-doct., UC San Diego
- 2007-2010 Research Associate, Scripps Research Institute
- 2010-now Professor, Zhejiang University

Research:

- ◆ Transition metal-catalyzed transformations and their application in the synthesis of natural products
- ◆ Development of new reactions and auxiliaries for C-H bond functionalization

Contents



Introduction



Palladium-Catalyzed Asymmetric C-H Olefination



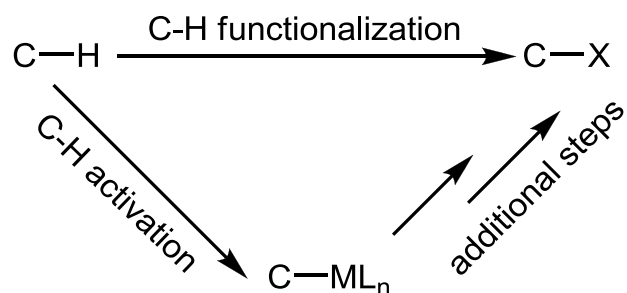
Palladium-Catalyzed Asymmetric C-H Alkynylation



Summary

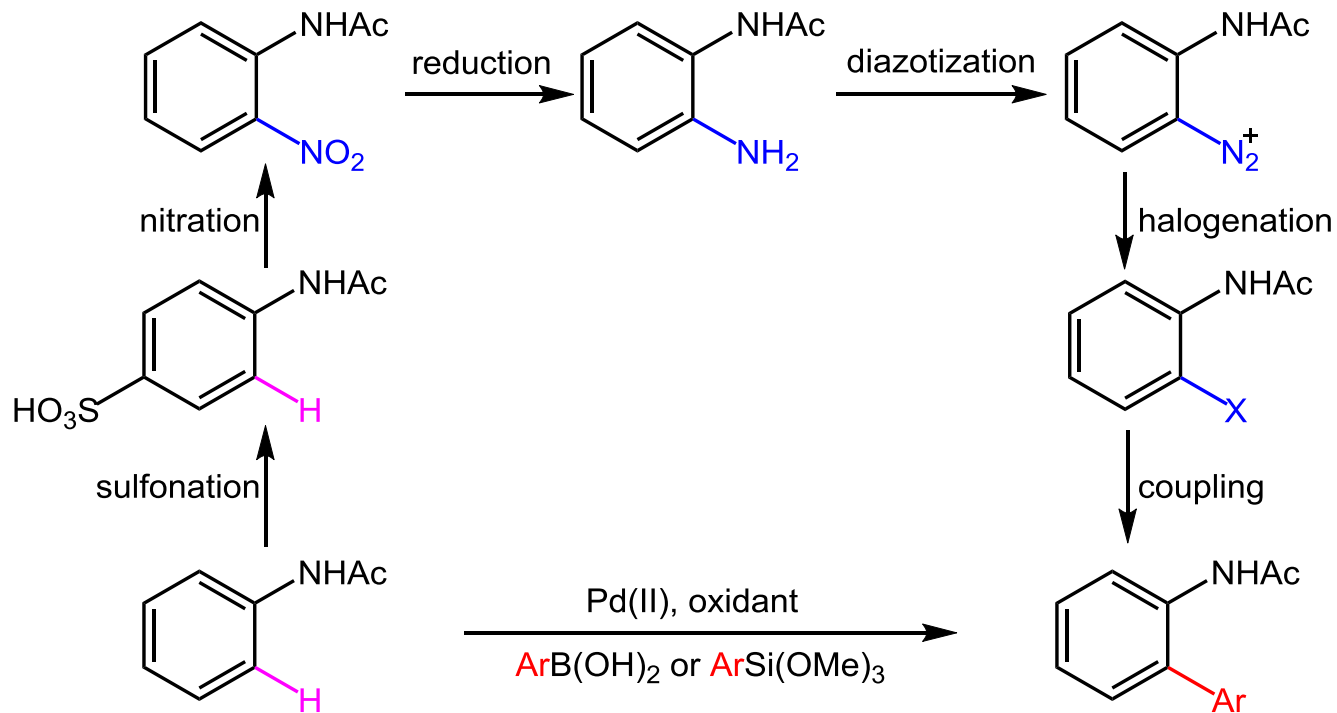
Introduction

Carbon–hydrogen bond functionalization (C–H functionalization) is a type of reaction in which a **carbon-hydrogen bond** is cleaved and replaced with a carbon-X bond (where X is usually carbon, oxygen or nitrogen). The term usually implies that a transition metal is involved in the C-H cleavage process. Reactions classified by the term typically involve the **hydrocarbon** first to react with a metal catalyst to create an organometallic complex in which the hydrocarbon is coordinated to the inner-sphere of a metal, either *via* an intermediate "alkane or arene complex" or as a transition state leading to a "M–C" intermediate.



General scheme for C-H functionalization

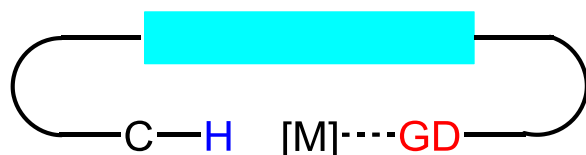
Introduction



Introduction

Two Strategies for Directed C-H Activation

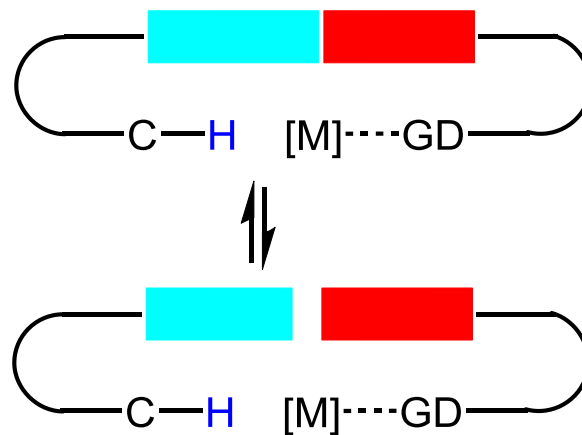
pre-installed directing groups



DG: directing group

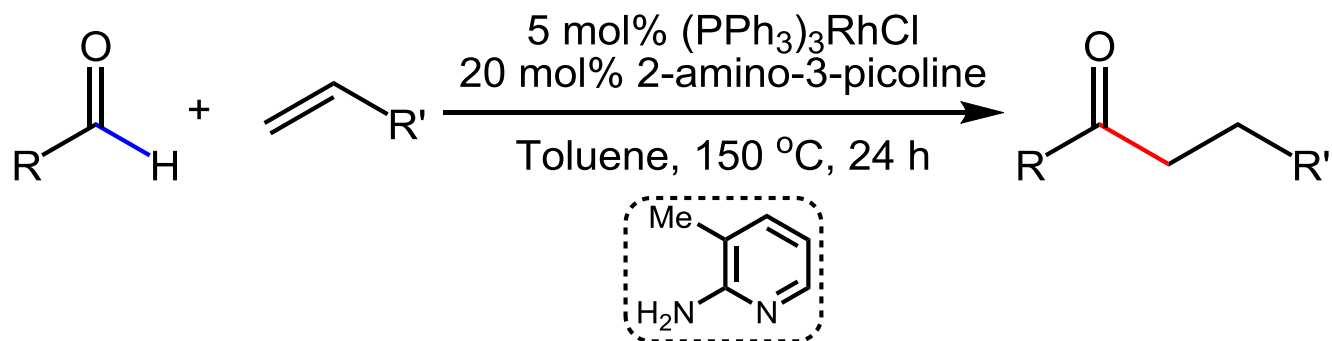
Disadvantage: requires installation and removal of the directing group

transient directing groups

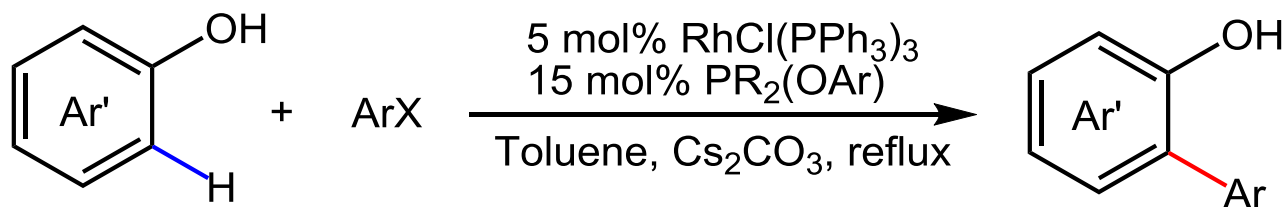


Yu, J.-Q. *et al.* *Science* **2016**, 351, 252.

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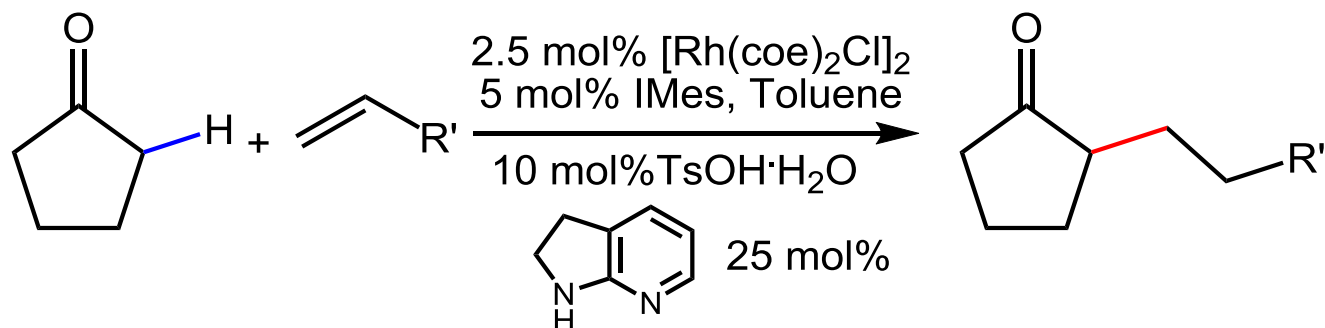


Jun, C.-H. et al. J. Org. Chem. 1997, 62, 1200.

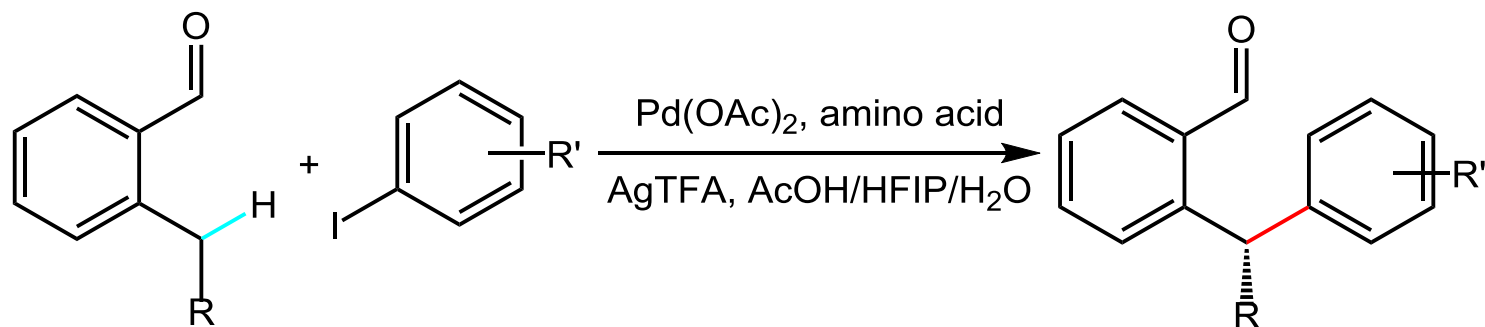


Bedford, R. B. et al. Angew. Chem. Int. Ed. 2003, 42, 112.

Introduction

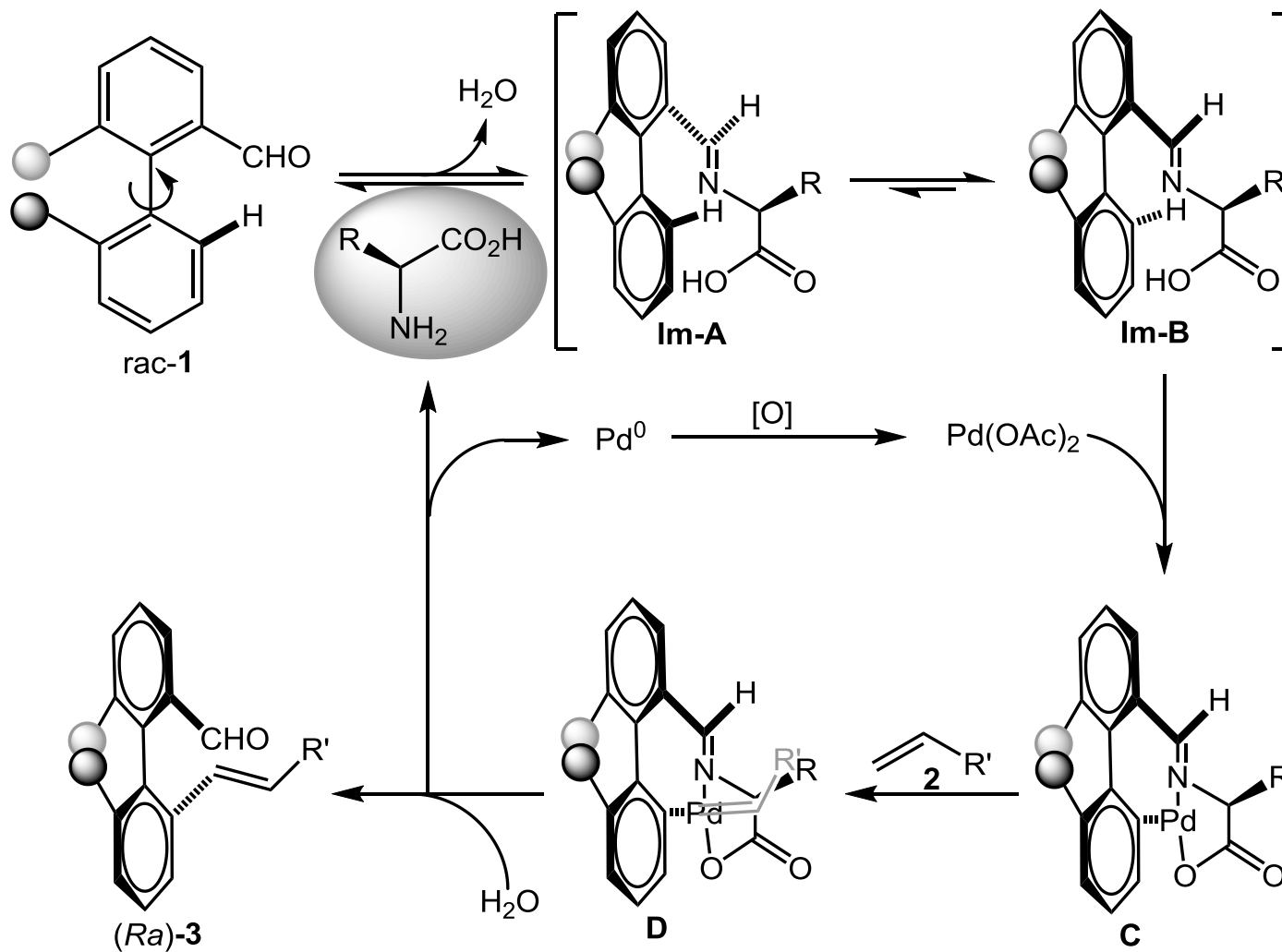


Dong, G. *et al. Science* **2014**, 345, 68.



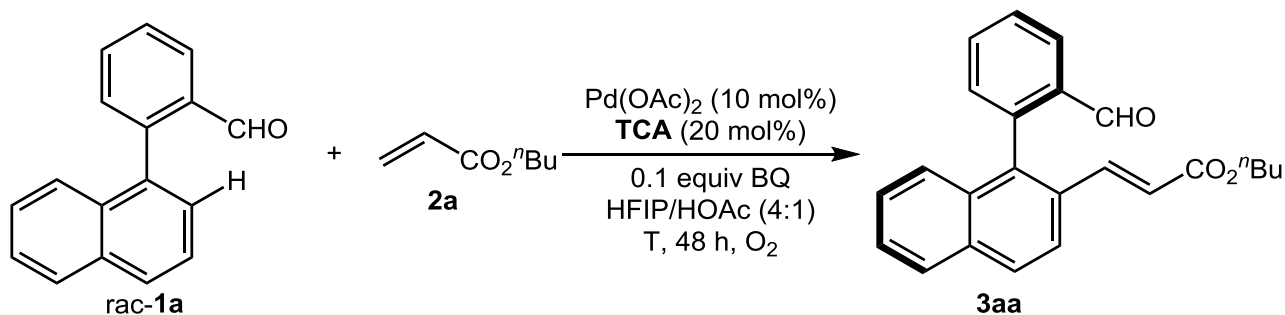
Yu, J.-Q. *et al. Science* **2016**, 351, 252.

Palladium-catalyzed asymmetric C-H olefination



Shi, B.-F. *et al.* *Angew. Chem. Int. Ed.* **2017**, *56*, 6617.

Optimization of reaction conditions



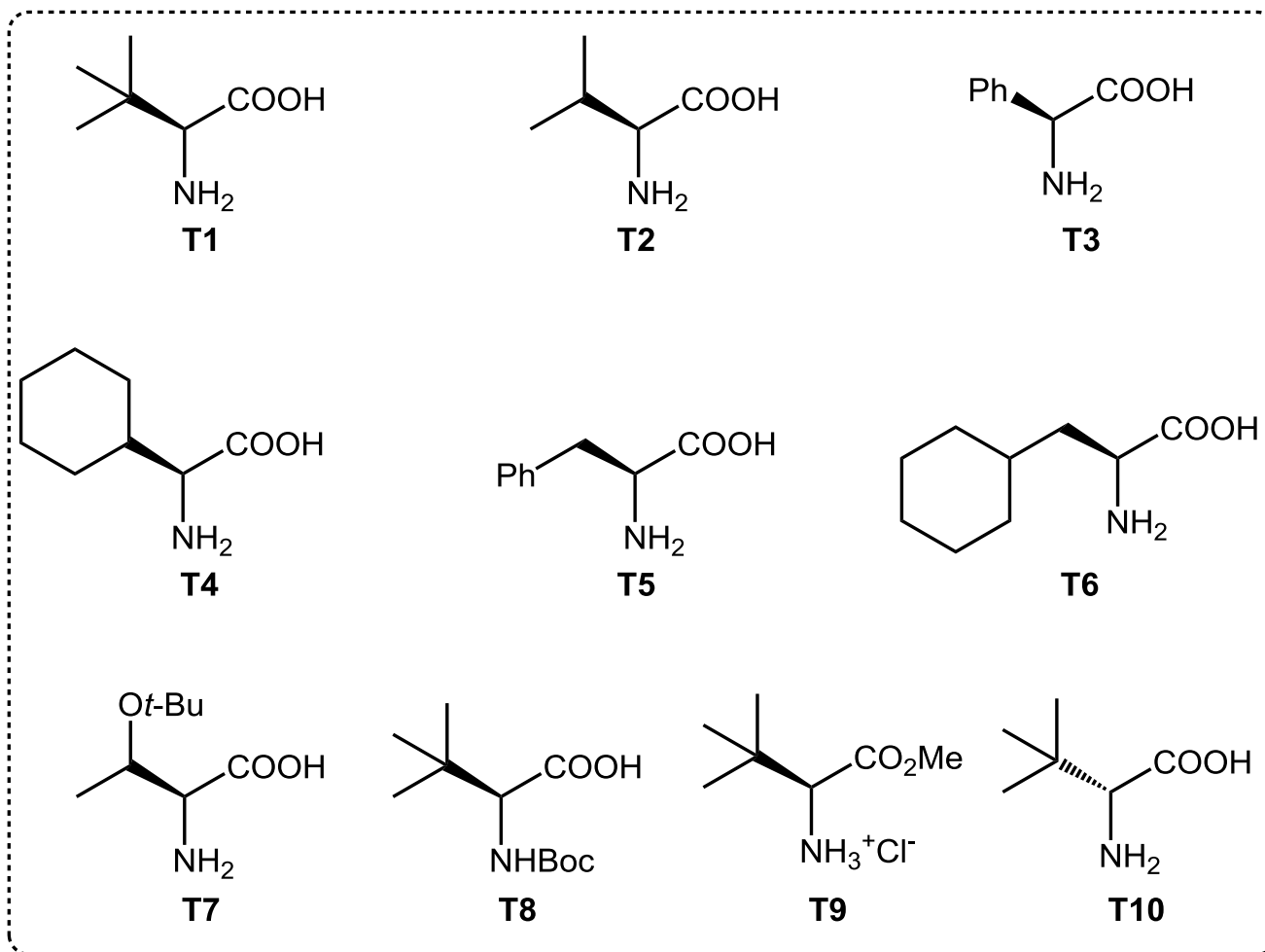
Entry	TCA	T (°C)	Yield (%) ^b	ee (%) ^c
1	T1	90	83	63
2	T1	80	86	89
3	T1	70	90	92
4	T1	60	92 (90)^d	99
5	T2	60	81	63

Optimization of reaction conditions

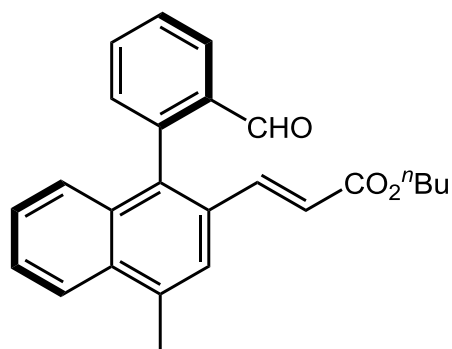
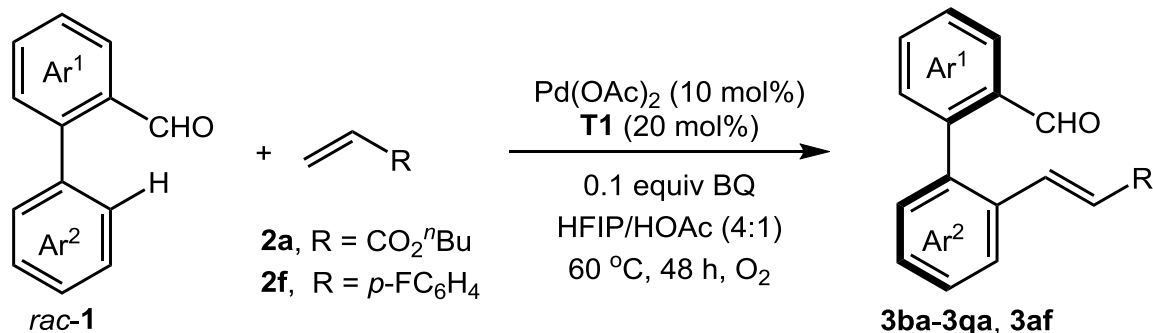
Entry	TCA	Yield (%) ^b	ee (%) ^c
6	T3	30	32
7	T4	70	11
8	T5	63	67
9	T6	68	40
10	T7	58	29
11	-	0	-
12	T8	trace	-
13	T9	0	-
14	T10	94 (93) ^d	-99

^a Reaction conditions: rac-**1a** (0.1 mmol), **2a** (3.0 equiv), Pd(OAc)₂ (0.1 equiv), TCA (0.2 equiv), BQ (0.1 equiv) in HFIP/HOAc (4:1, v/v, 1 mL) under O₂ for 48 h. ^b Determined by ¹HNMR spectroscopy using dibromomethane as the internal standard. ^c The ee value was determined by HPLC. ^d Yield of isolated product is within parentheses.

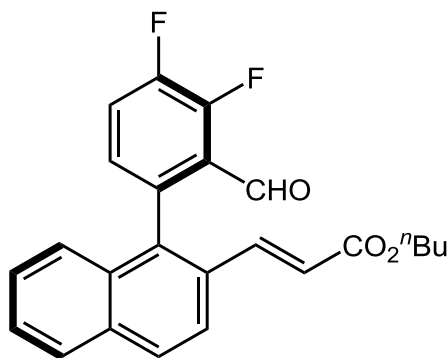
Chiral amino acids



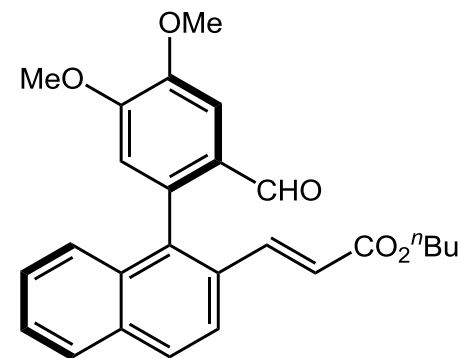
Palladium-catalyzed C-H olefination/DKR of biaryls



3ba 90%, 98% ee

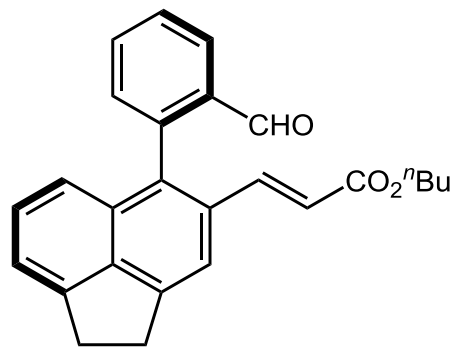


3ca 72%, 98% ee

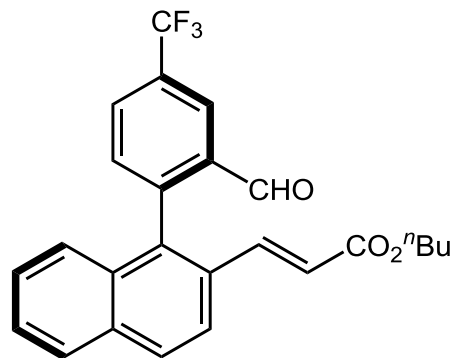


3da 65%, >99% ee

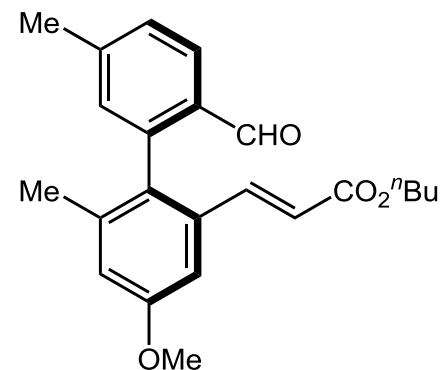
Palladium-catalyzed C-H olefination/DKR of biaryls



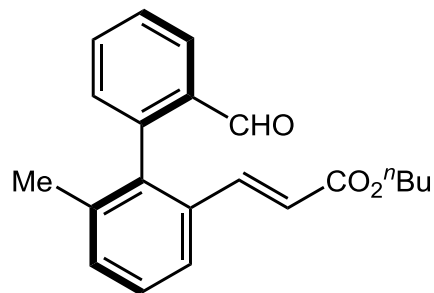
3ea 98%, 97% ee



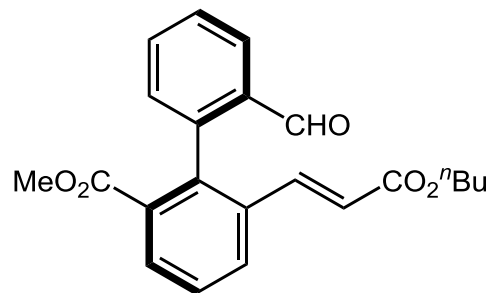
3fa 90%, 99% ee



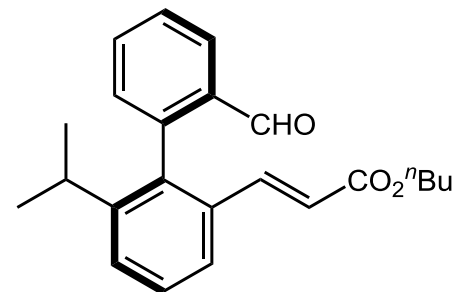
3ga 98%, 98% ee



3ha 88%, 97% ee

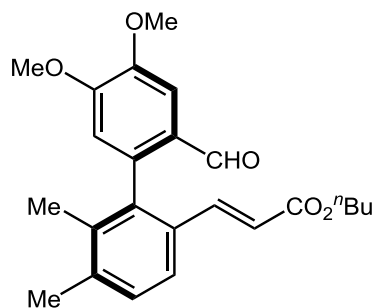


3ia 65%, >99% ee

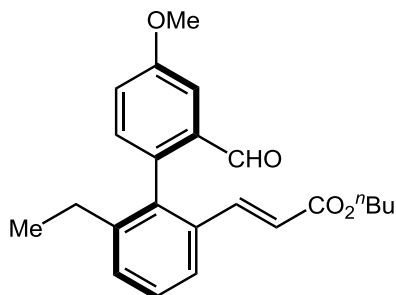


3ja 94%, 97% ee

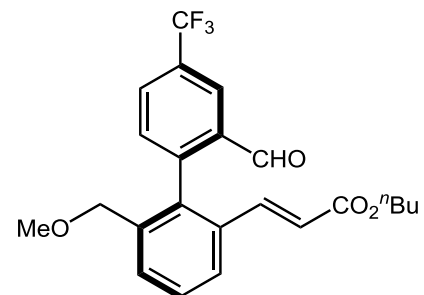
Palladium-catalyzed C-H olefination/DKR of biaryls



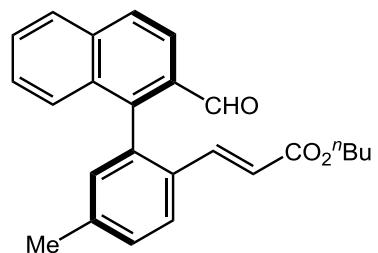
3ka 95%, 99% ee



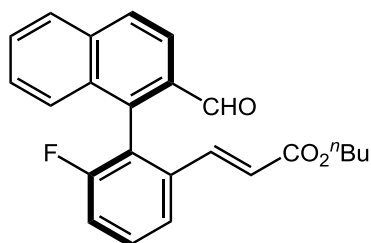
3la 94%, 98% ee



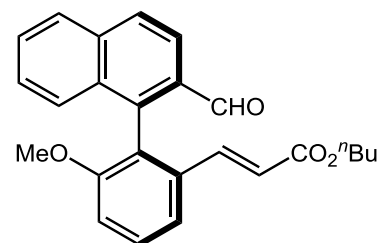
3ma 89%, 95% ee



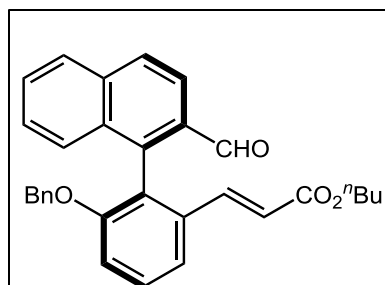
3na 85%, 98% ee



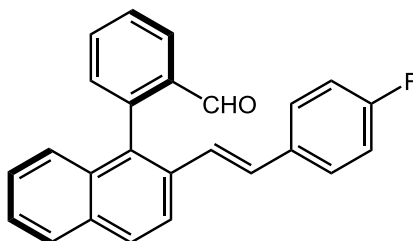
3oa 44%, >99% ee



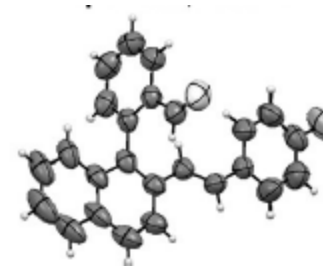
3pa 70%, >99% ee



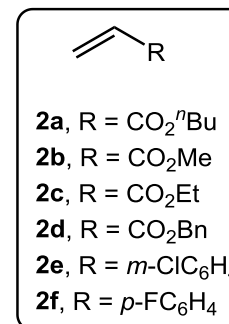
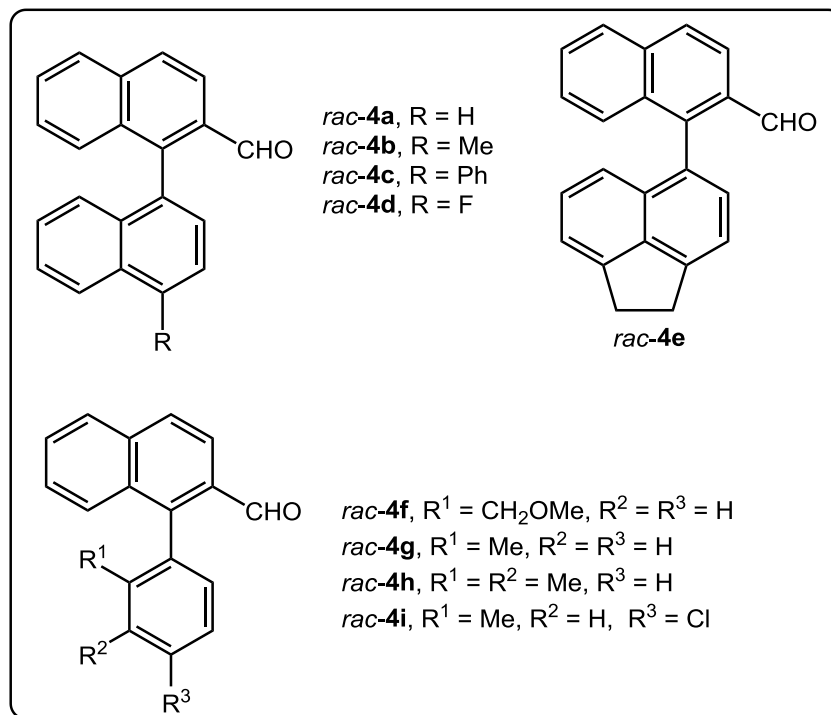
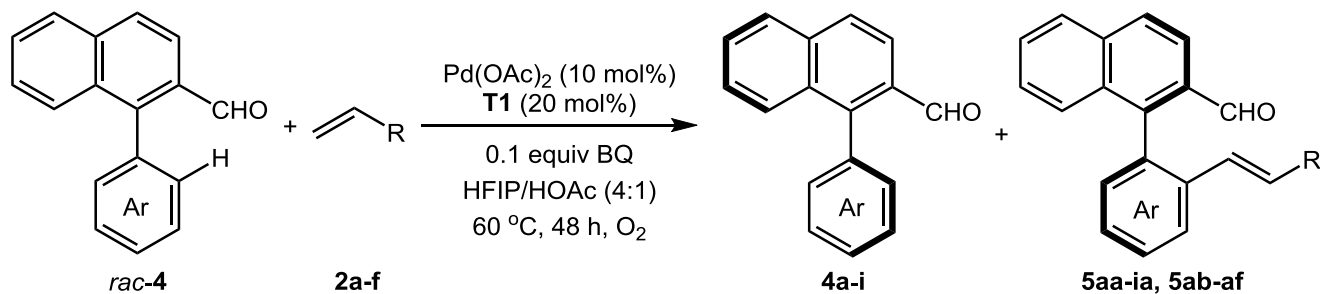
3qa 60%, 99% ee



3af 83%, 97% ee



Palladium-catalyzed C-H olefination/KR of biaryls



Palladium-catalyzed C-H olefination/KR of biaryls

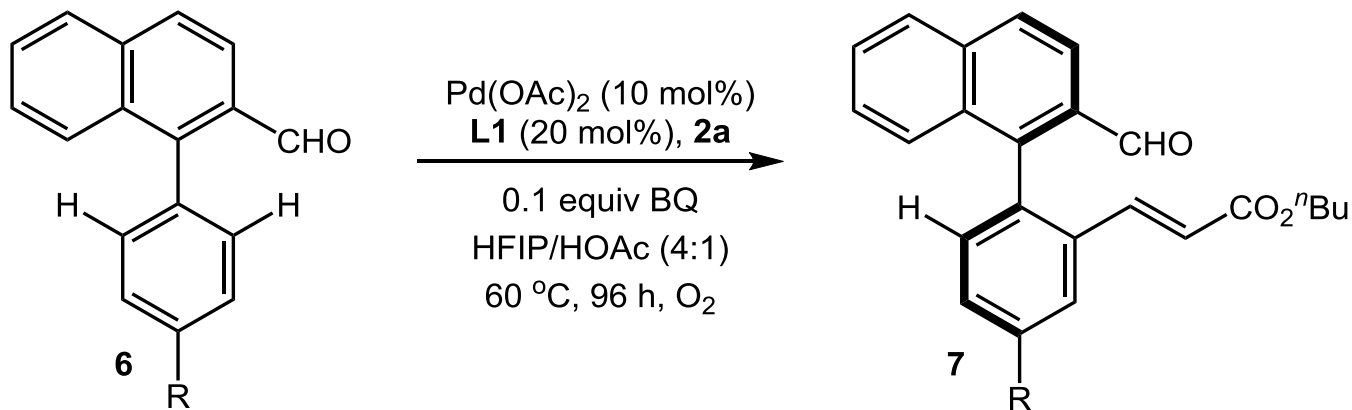
Entry	rac-4	5	4 Yield (%) ^a	4 ee (%) ^b	5 Yield (%) ^a	5 ee (%) ^b	S ^c
1	4a	5aa	51	79	42	>99	483
2	4b	5ba	56	73	44	99	438
3	4c	5ca	54	89	46	>99	600
4	4d	5da	43	87	41	95	111
5	4e	5ea	46	97	46	97	278
6	4f	5fa	55	76	45	98	227
7	4g	5ga	63 (50)	60 (87)	37 (43)	95 (98)	72 (283)
8	4h	5ha	45	69	30	95	81
9	4i	5ia	60	70	40	99	419

Palladium-catalyzed C-H olefination/KR of biaryls

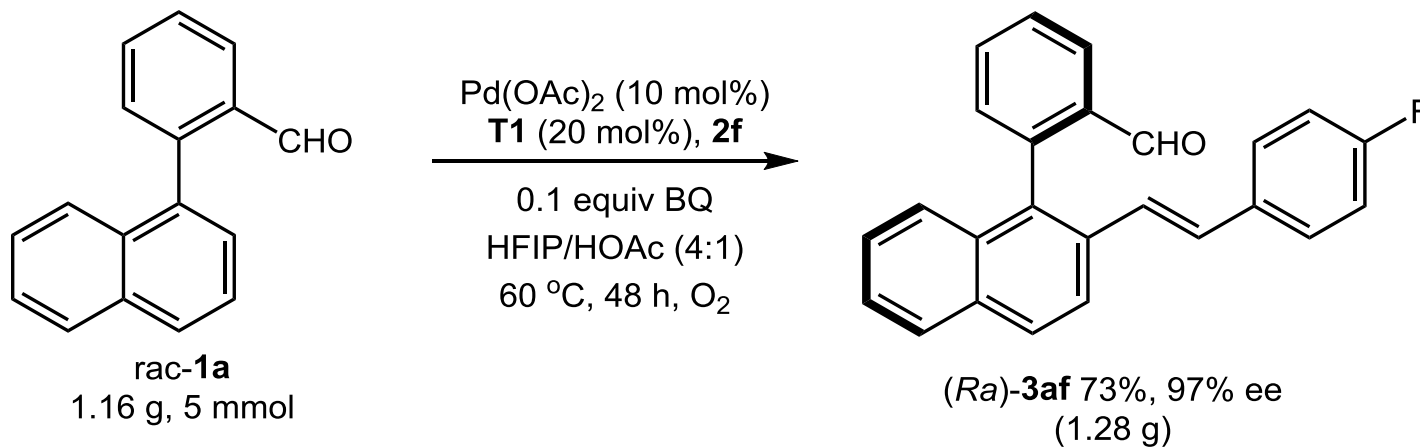
Entry	rac-4	5	4 Yield (%) ^a	4 ee (%) ^b	5 Yield (%) ^a	5 ee (%) ^b	S ^c
10	4a	5ab	55	69	45	99	413
11	4a	5ac	47	95	47	95	146
12	4a	5ad	60	69	37	>99	413
13 ^d	4a	5ae	57 (49)	61 (96)	40 (49)	98 (98)	185 (392)
14 ^d	4a	5af	57 (48)	67 (87)	40 (41)	95 (>99)	79 (570)

^a Yield of isolated product. ^b The ee value was determined by HPLC. ^c $S = \ln[(1-C)(1-ee_4)]/\ln[(1-C)(1+ee_4)]$, $C = ee_4/(ee_4+ee_5)$. ^d Data within parentheses is for reaction run for 96 h.

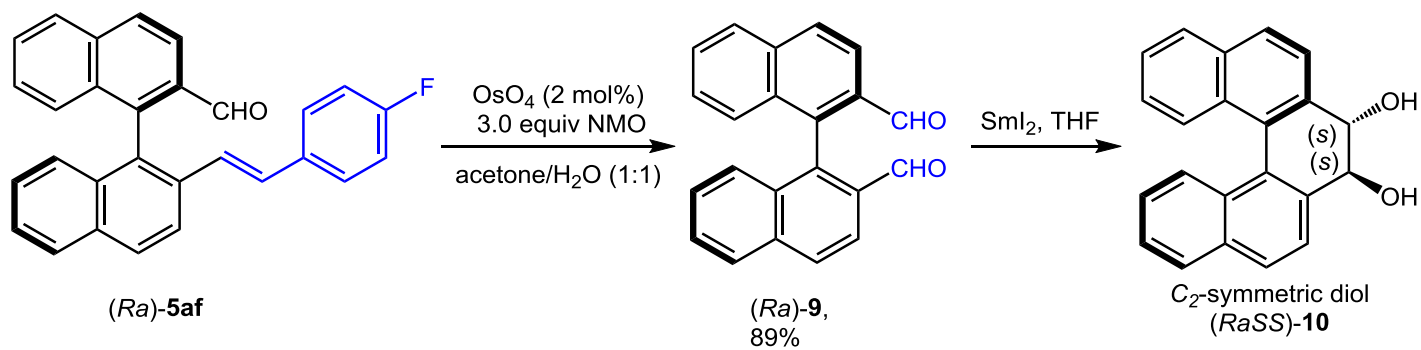
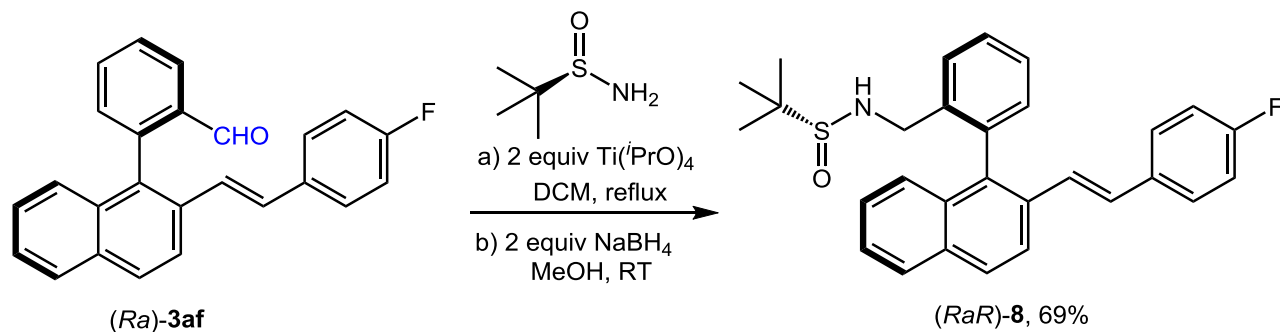
Desymmetrization of proaxially biaryls & gram scale



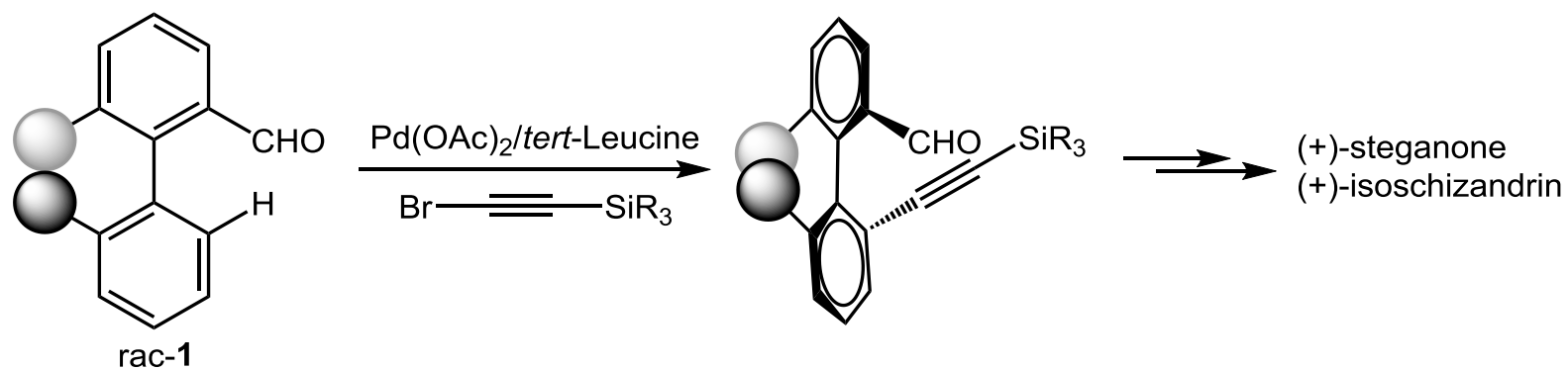
7aa, R = Me, 93%, 99% ee
7ba, R = OMe, 89%, 99% ee
7ca, R = Cl, 90%, 99% ee
7da, R = F, 95%, 99% ee



Syntheses of chiral ligands & chiral diol

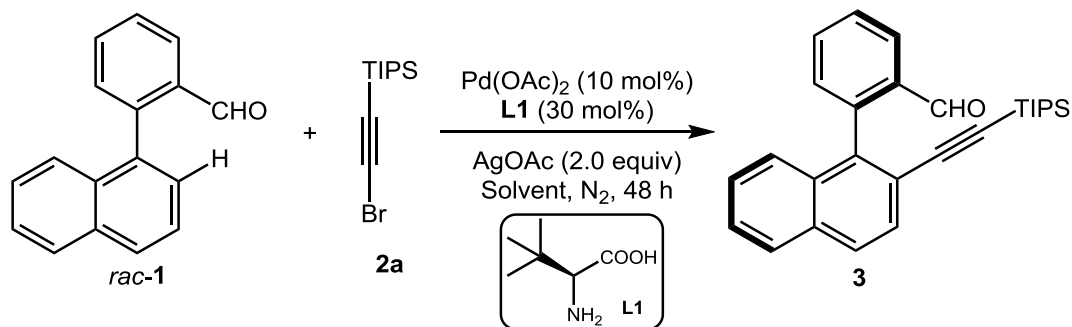


Palladium-catalyzed atroposelective C-H alkylation



Shi, B.-F. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 3661.

Effects of the solvents on the reaction outcome



Entry	Solvent	Yield (%) ^b	ee (%) ^c
1	Toluene	0	-
2	1,4-dioxane	trace	-
3	HFIP	6	98
4	HOAc	56	98
5 ^d	HOAc	12	98

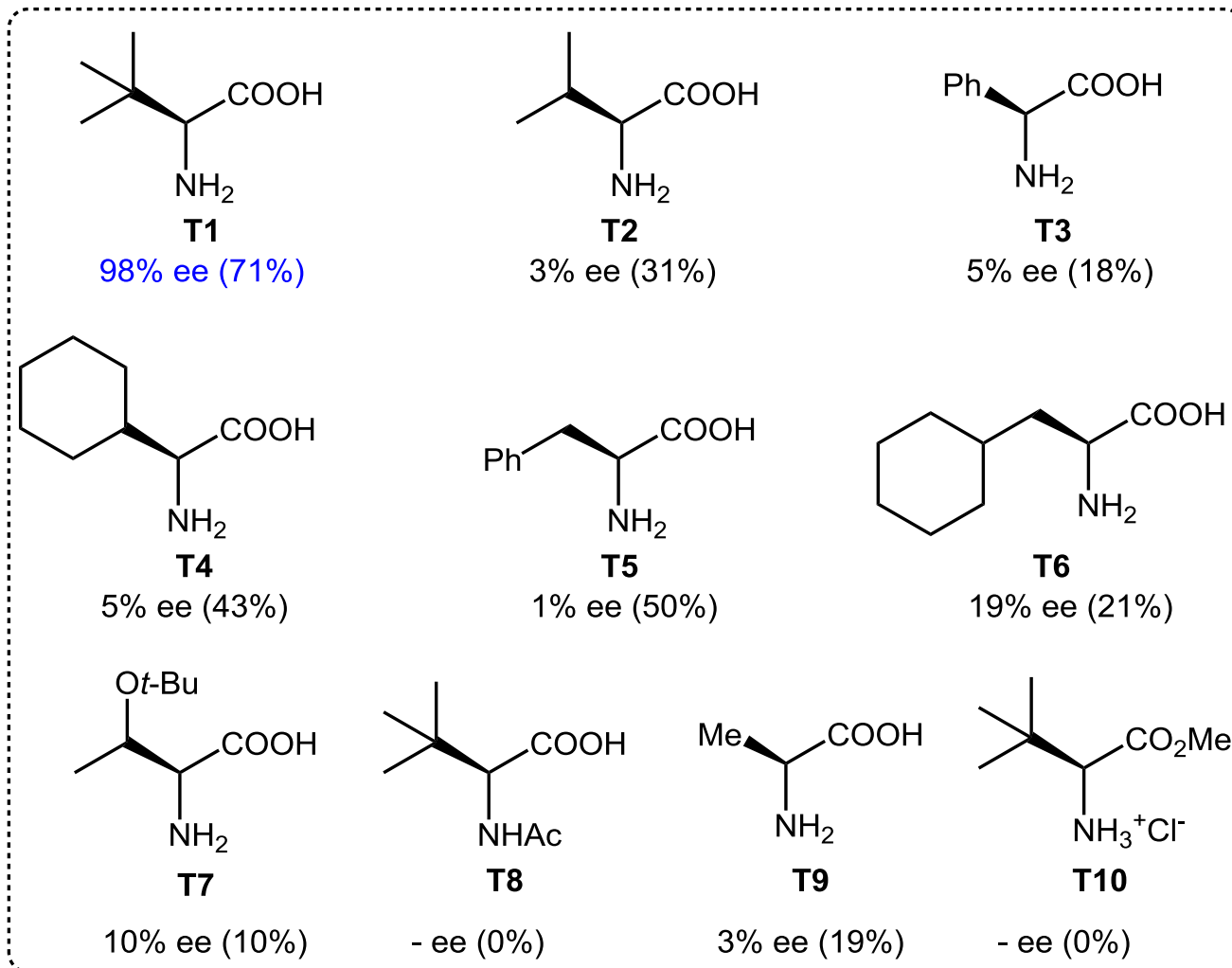
^a *rac-1a* (0.1 mmol), **2a** (3.0 equiv), Pd(OAc)₂ (0.1 equiv), **L1** (0.3 equiv), AgOAc (2.0 equiv), solvent (1.0 mL), 60 °C, N₂, 48 h. ^b Isolated yield. ^c The ee value was determined by HPLC. ^d Without AgOAc.

Effects of the additives on the reaction outcome

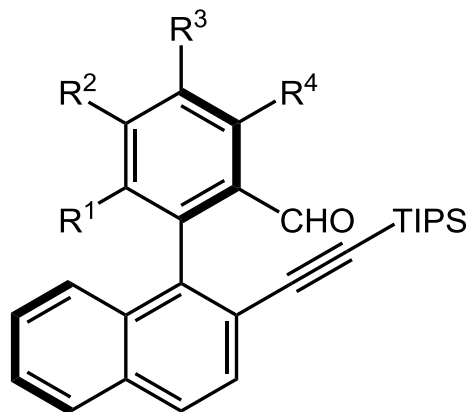
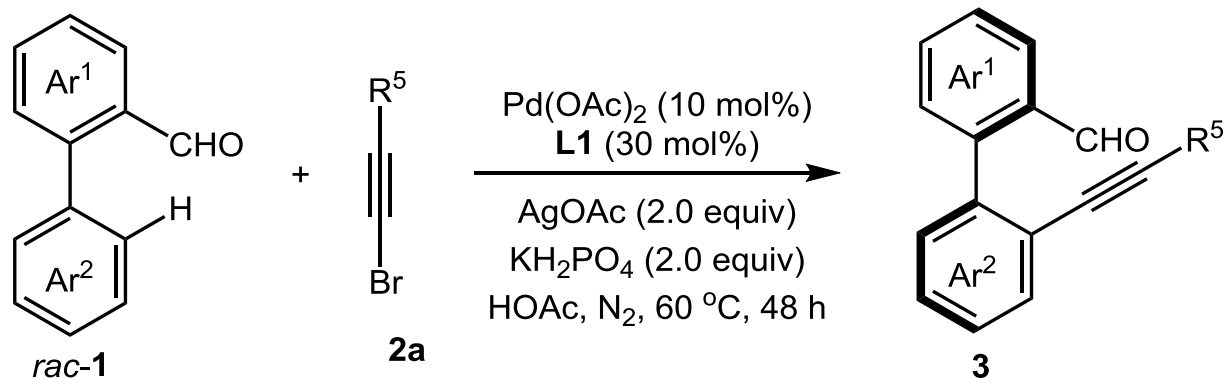
Entry	Additives	Yield (%) ^b	ee (%) ^c
1	NaOEt	22	94
2	NaOAc	39	94
3	NaTFA	40	98
4	NaF	11	99
5	NaNO ₃	44	98
6	LiH ₂ PO ₄	66	98
7	NaH ₂ PO ₄	60	98
8	KH ₂ PO ₄	71	98

^a rac-**1a** (0.1 mmol), **2a** (3.0 equiv), Pd(OAc)₂ (0.1 equiv), **L1** (0.3 equiv), AgOAc (2.0 equiv), additive (2.0 equiv), HOAc (1.0 mL), 60 °C, N₂, 48 h. ^b Isolated yield. ^c The ee value was determined by HPLC.

Effects of the amino acids on the reaction outcome

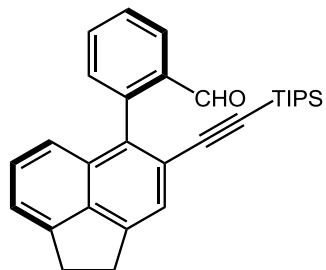


Palladium-catalyzed C-H alkynylation/DKR of biaryls

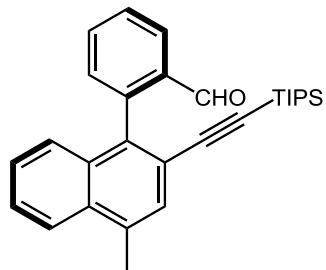


- 3b**, $R^1 = R^2 = R^4 = \text{H}$, $R^3 = \text{CF}_3$, 63%, >99% ee
3c, $R^1 = R^2 = R^4 = \text{H}$, $R^3 = \text{OMe}$, 88%, 91% ee
3d, $R^1 = R^2 = R^4 = \text{H}$, $R^3 = \text{F}$, 61%, 95% ee
3e, $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{Cl}$, 75%, 93% ee
3f, $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{Me}$, 70%, 93% ee
3g, $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{F}$, 67%, 93% ee
3h, $R^1 = R^2 = R^3 = \text{H}$, $R^4 = \text{F}$, 80%, 91% ee
3i, $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{F}$, 84%, 94% ee
3j, $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{OMe}$, 91%, 91% ee
3k, $R^1 = R^4 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{F}$, 65%, 94% ee
3l, $R^1 = \text{F}$, $R^2 = R^3 = R^4 = \text{H}$, 62%, 93% ee
3m, $R^1 = R^2 = R^3 = \text{OMe}$, $R^4 = \text{H}$, 73%, 98% ee

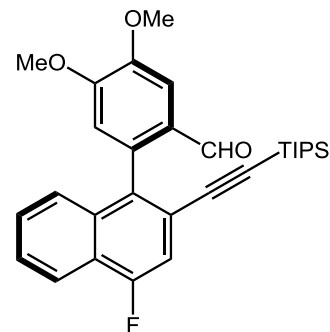
Palladium-catalyzed C-H alkynylation/DKR of biaryls



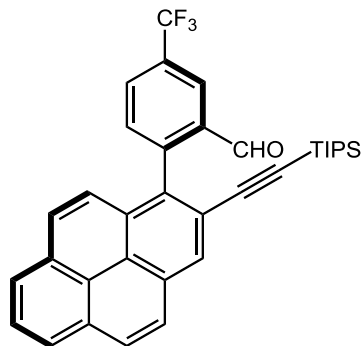
3n 82%, 95% ee



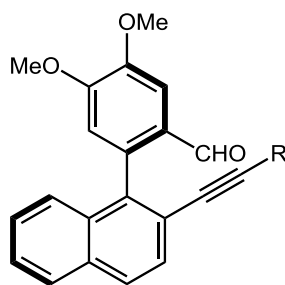
3o 72%, >99% ee



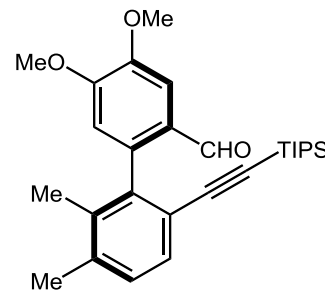
3p 65%, 90% ee



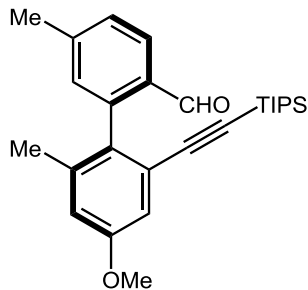
3q 84%, 94% ee



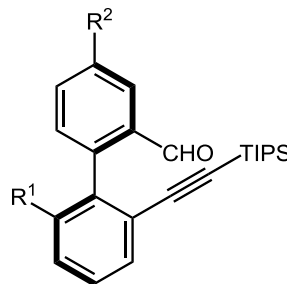
3r R = TES, 45%, 99% ee
3s R = TBS, 74%, 99% ee



3t 52%, 98% ee



3o 61%, 97% ee



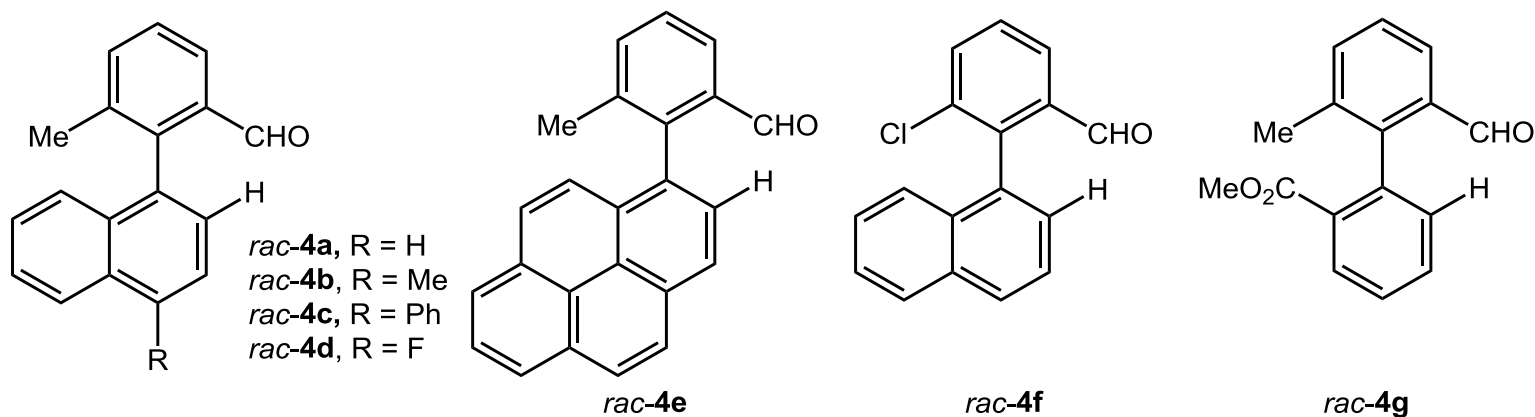
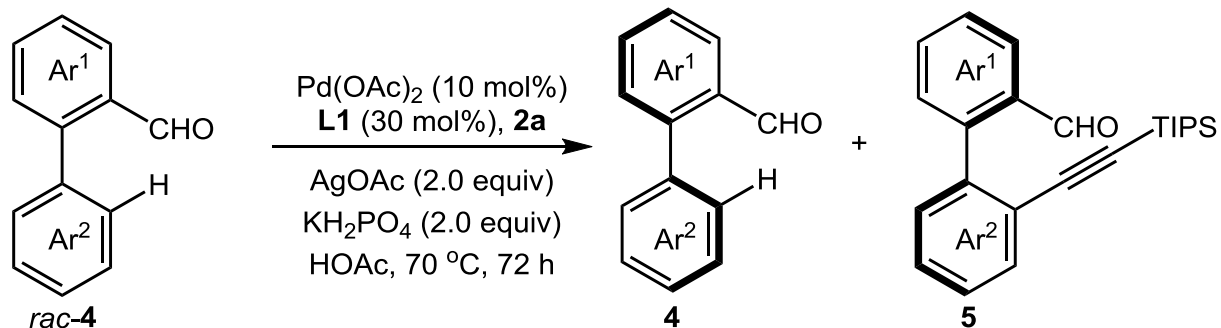
3m, R¹ = CO₂Me, R² = H, 60%, 96% ee

3w, R¹ = *i*Pr, R² = H, 61%, 90% ee

3x, R¹ = CH₂OMe, R² = OMe, 63%, 91% ee

3y, R¹ = CF₃, R² = OMe, 42%, 98% ee

Palladium-catalyzed C-H olefination/KR of biaryls

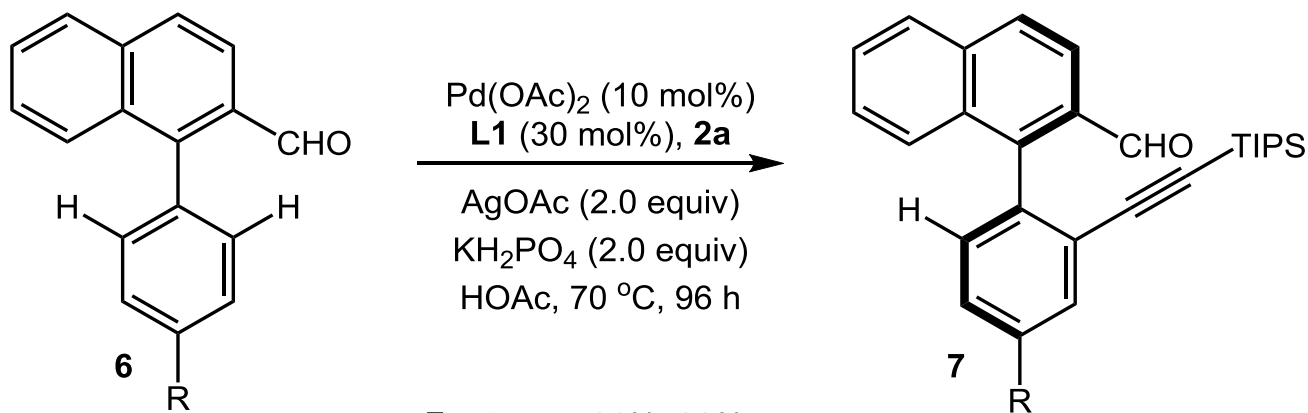


Palladium-catalyzed C-H alkynylation/KR of biaryls

Entry	<i>rac</i> -4	5	4 Yield (%) ^a	4 ee (%) ^b	5 Yield (%) ^a	5 ee (%) ^b	S ^c
1	4a	5a	49	90	42	96	152
2	4b	5b	53	68	40	96	100
3	4c	5c	50	95	43	96	183
4	4d	5d	44	97	43	93	116
5	4e	5e	53	75	35	98	224
6	4f	5f	46	89	46	99	600
7	4g	5g	61	63	31	98	190

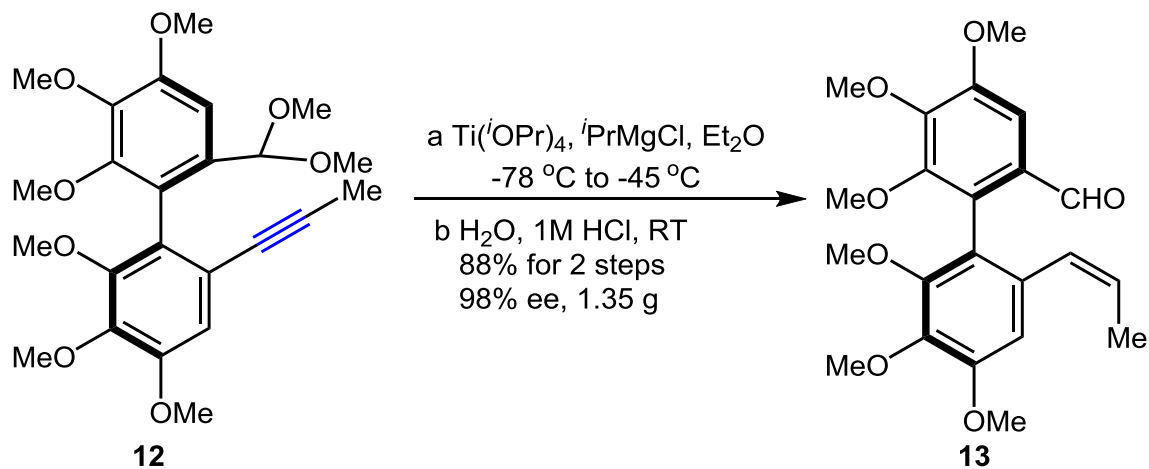
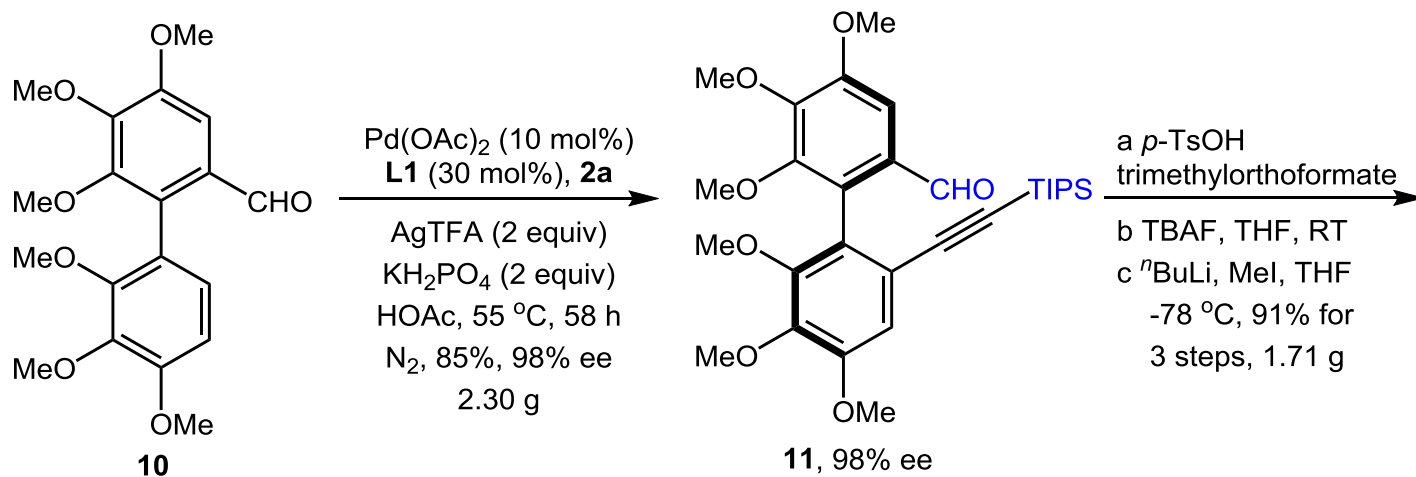
^a Yield of the isolated product. ^b The ee value was determined by HPLC. The absolute configuration of the enantiomerically enriched products and starting materials was assigned by analogy with **3**. ^c $S = \ln[(1-C)(1-ee_4)]/\ln[(1-C)(1+ee_4)]$, $C = ee_4/(ee_4+ee_5)$.

Desymmetrization of proaxially biaryls

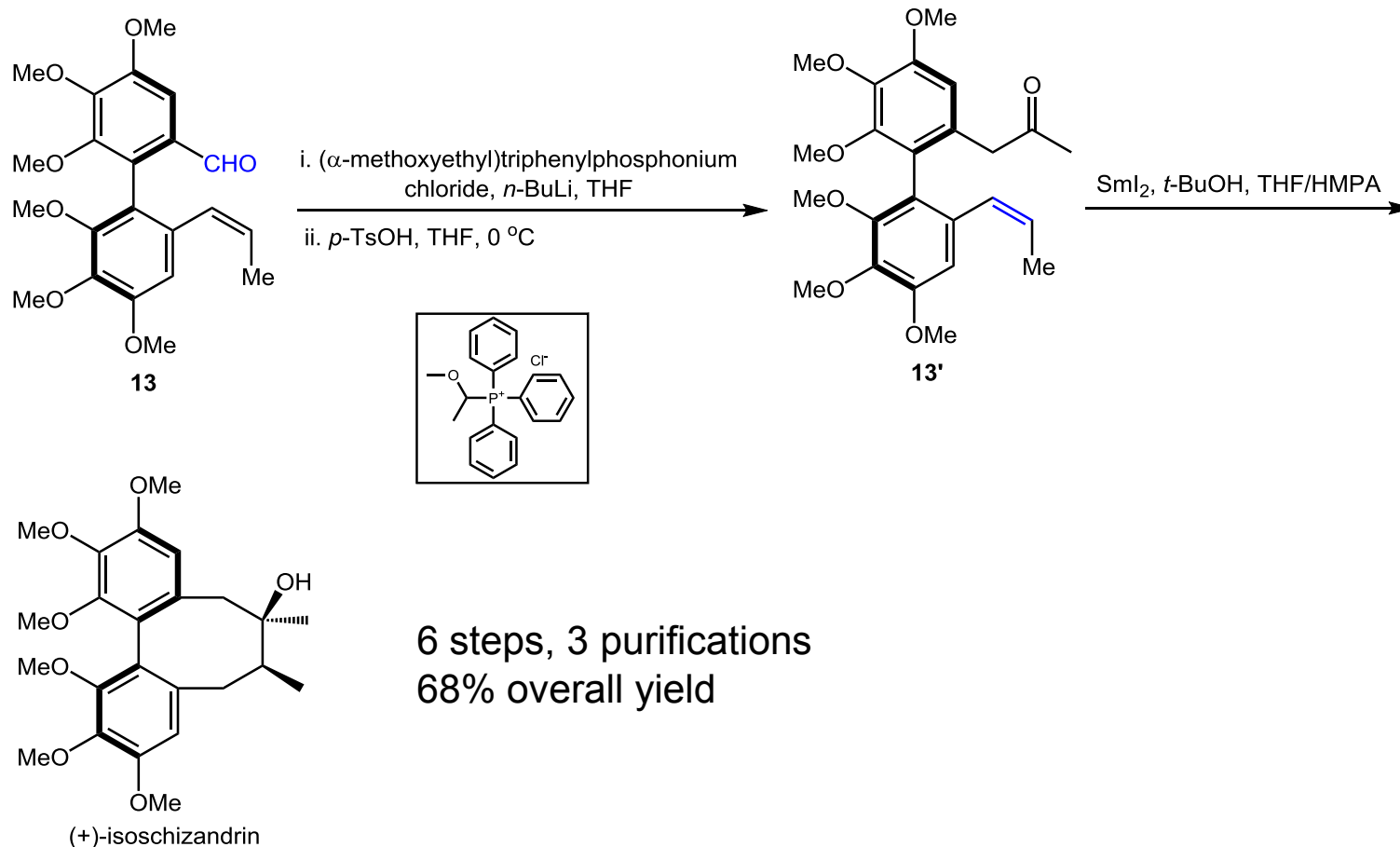


- 7a**, R = H, 61%, 90% ee
- 7b**, R = F, 55%, 94% ee
- 7c**, R = Cl, 54%, 92% ee
- 7d**, R = Me, 61%, 94% ee
- 7e**, R = OMe, 65%, 91% ee

Formal synthesis of (+)-isoschizandrin

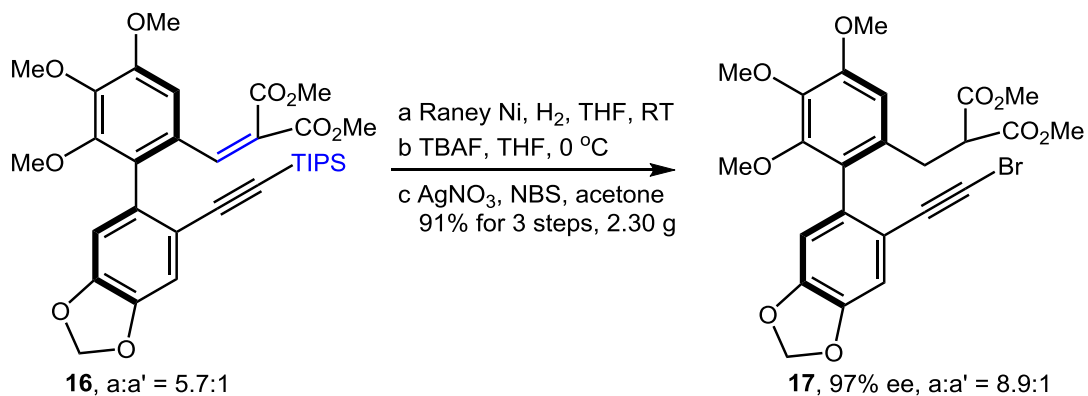
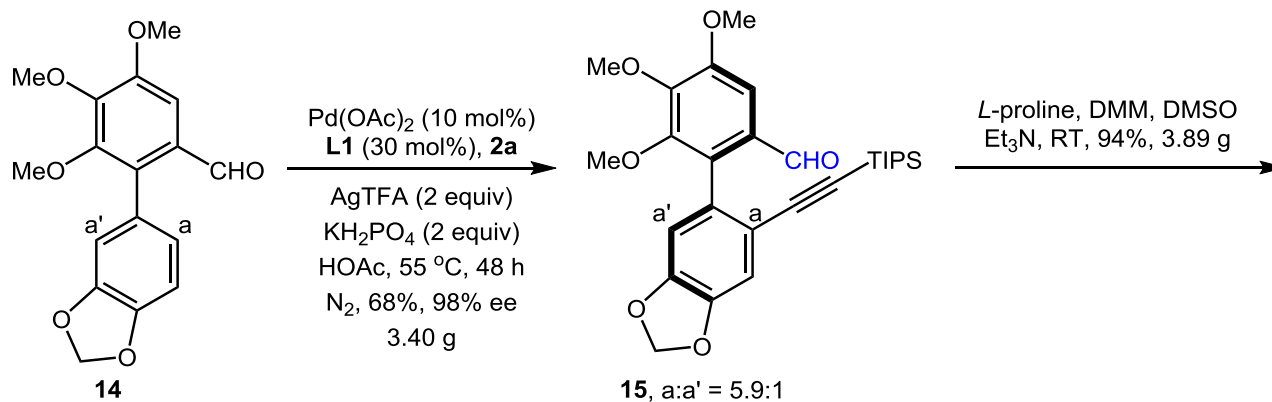


Formal synthesis of (+)-isoschizandrin

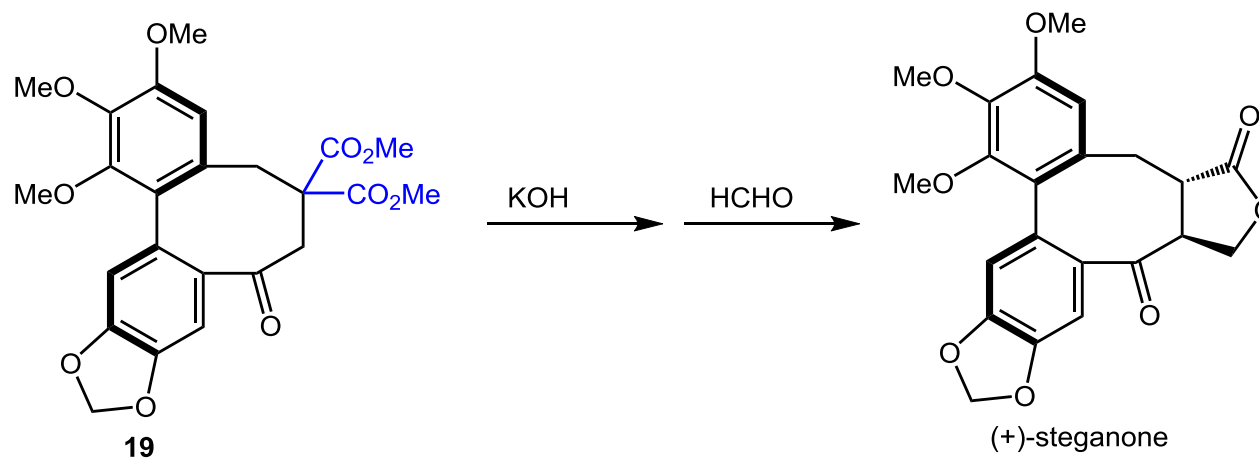
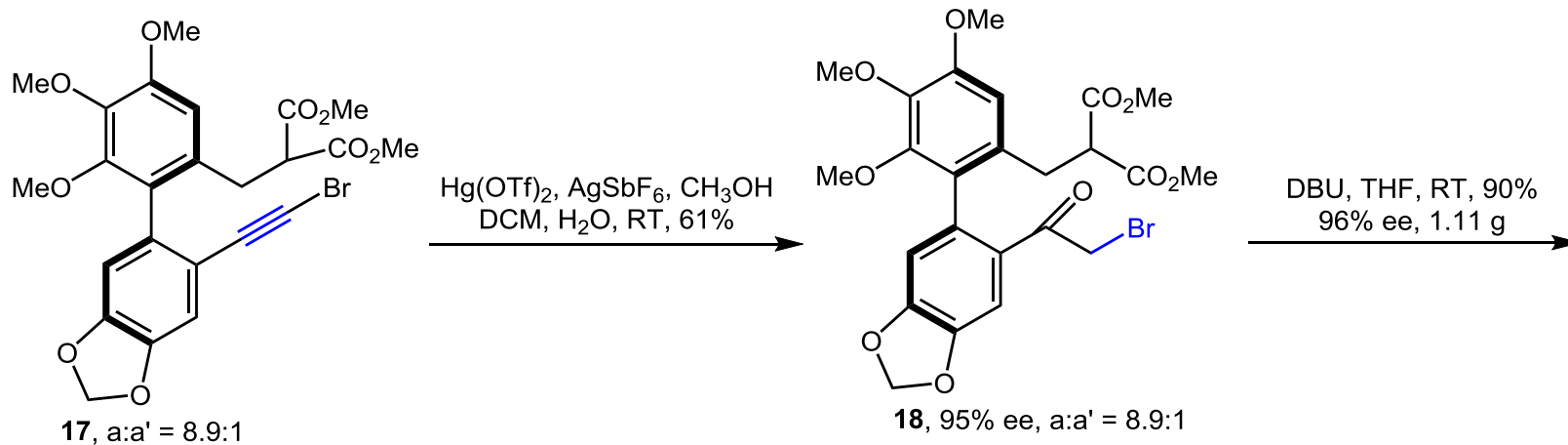


6 steps, 3 purifications
68% overall yield

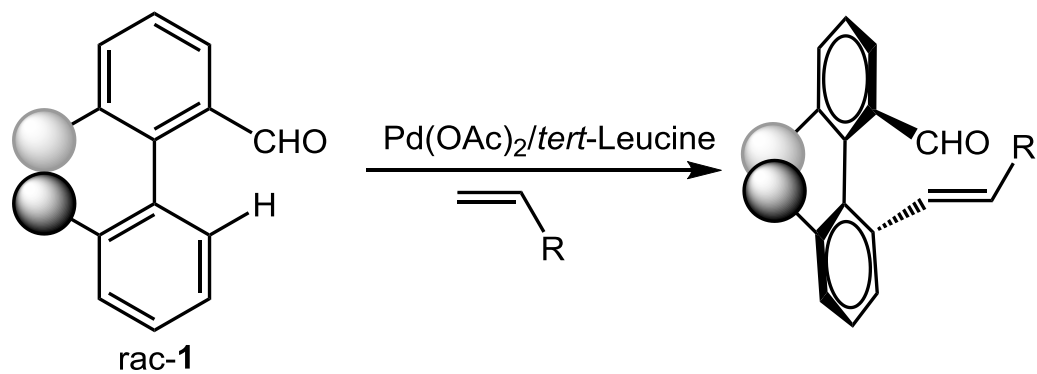
Formal synthesis of (+)-steganone



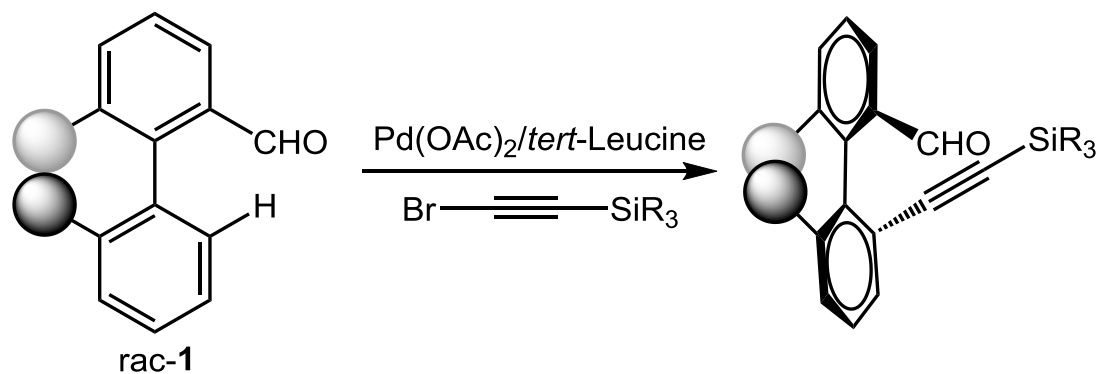
Formal synthesis of (+)-steganone



Summary



Shi, B.-F. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 6617.



Shi, B.-F. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 3661.

The First Paragraph

Dibenzocyclooctadiene lignans are a common class of natural products that possess unique structural features and significant biological activity. For example, (+)-isoschizandrin and its analogues, which originate from *Schizandra chinensis*, a fruit in northern China, were used as an antitussive and a tonic in Chinese and Japanese traditional medicine. (-)-Steganone was isolated along with related compounds from *Steganotaenia araliacea* by Kupchan *et al.* in 1973 and reported to have significant activity against P-388 leukemia in mice and excellent bioactivity *in vitro* against cells derived from human carcinoma of the nasopharynx. The key axially chiral biaryl core structures of these dibenzocyclooctadiene lignans are interesting targets but also represent bottlenecks for total synthesis.

The First Paragraph

A number of elegant synthetic pathways have been developed for these lignans, whereby some of the approaches require a stoichiometric amount of chiral reagents and suffer from low overall yield, poor step-economy, and/or moderate stereocontrol. Furthermore, these synthetic routes are limited to a milligram scale; the ultimate challenge of producing large quantities of these lignans for biological evaluation has yet to be surmounted. Our goal was to establish a modular, scalable, and generally applicable strategy for the atroposelective construction of the biaryl core structures that would provide rapid access to large quantities of related lignans and offer the opportunity to elucidate their biological features.

The Last Paragraph

In conclusion, we have demonstrated the remarkable synthetic potential of a palladium-catalyzed atroposelective C-H alkynylation strategy in natural product syntheses. *tert*-Leucine was used as a key catalytic transient chiral auxiliary. A broad range of enantiomerically enriched biaryl compounds were obtained in good yields with excellent enantioselectivity. Gram-scale, stereocontrolled formal syntheses of (+)-isoschizandrin and (+)-steganone were achieved based on this method. These syntheses compare very favorably with previous syntheses in terms of step economy, overall yield, and stereocontrol. Further applications of this method to the synthesis of other dibenzocyclooctadiene lignan analogues and axially chiral biaryl compounds are in progress.