Published in final edited form as:

Adv Synth Catal. 2011 November 1; 353(17): 3123–3128. doi:10.1002/adsc.201100447.

Cinchona alkaloid catalyzed enantioselective amination of α,β -unsaturated ketones: an asymmetric approach to Δ^2 -pyrazolines

Nathaniel R. Campbell^a, Bingfeng Sun^a, Ravi P. Singh^a, and Li Deng^a

Li Deng: deng@brandeis.edu

^aDepartment of Chemistry, Brandeis University, 415 South St., Waltham, MA 02454-9110, USA, Fax: (+1)-781-736-2516

Abstract

Δ^2 -Pyrazolines are of significant medicinal and synthetic interest due to their therapeutic properties and utility in the synthesis of 1,3-diamines, yet few asymmetric methods exist to prepare them. An unprecedented highly enantioselective organocatalytic synthesis of 2-pyrazolines was achieved through an asymmetric conjugate addition catalyzed by 9-*epi*-amino cinchona alkaloids followed by deprotection-cyclization, which furnished chiral 2-pyrazolines in 46–78% yield and 59–91% ee. This bifunctional catalytic methodology thus provides easy access to considerable range of optically active 3,5-dialkyl 2-pyrazolines.

Keywords

asymmetric catalysis; Δ^2 -Pyrazolines; cinchona alkaloids; conjugate addition reaction; cyclization; enones

Δ^2 -Pyrazolines and their derivatives have been reported to possess antimicrobial,^[1] immunosuppressive,^[2] anti-cancer,^[3] antidepressant,^[4] and central nervous system effects.^[5] More recently, compounds with a 2-pyrazoline (4,5-dihydropyrazole) backbone have been targeted as potent CB₁ receptor antagonists (Figure 1), which have exhibited anti-obesity activity (Ibipinabant **1**^[6]). Also 2-pyrazolines have demonstrated potential activity in several biological screens,^[7] eg optimized 2-pyrazoline **2** have shown excellent activity (IC₅₀ = 26 nM) against kinesin spindle protein; inhibitors of this protein constitute an unique strategy in cancer treatment.^[8] Apart from their medicinal significance, 2-pyrazolines have also been shown as useful intermediates in the synthesis of various amines including pyrazolidines,^[9] azaproline,^[10] and 1,3-diamines.^[11]

To date, however, only a few examples have been reported of the asymmetric synthesis of chiral 2-pyrazolines, and optically pure 2-pyrazolines are commonly obtained by resolution of racemic counterparts.^[12] In 2000, the first asymmetric catalytic synthesis of 2-pyrazolines through the 1,3-dipolar cycloaddition of acrylamides was reported utilizing a chiral Lewis acid catalyst.^[13] In 2005 an indirect strategy to synthesize chiral 2-pyrazoline **3** (Figure 1) was reported where chirality was introduced by enantioselective organocatalytic thia-Michael addition to enones. However, 2-pyrazolines obtained by further transformation of the thia-adduct showed low ee's, and were found to readily undergo racemization.^[14] Alternatively, organometallic approaches which cover asymmetric [3+2] cycloadditions of 1,3-dipoles such as diazoesters,^[15] nitrile imine dipole precursors^[16] to α,β -enones provide

Correspondence to: Li Deng, deng@brandeis.edu.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200#####>.

trisubstituted 3,5-dialkyl 2-pyrazolines **4** in high ee and yield. More recently List and Müller disclosed the use of chiral phosphoric acid catalysis to obtain 2-pyrazolines **5** in high enantioselectivity and yield through a 6π electrocyclization,^[17] however, dialkyl pyrazolines ($R^1 = \text{alkyl}$) proved challenging, and only one example was reported with low ee and yield. Building upon this work, Brière and coworkers employed a cinchona alkaloid-derived phase transfer catalyst to arrive at 3,5-diaryl pyrazolines with good ee and yield.^[18]

However, the substrate scope was restricted to aryl substituted α,β -unsaturated enones making it of limited use. Thus, development of an asymmetric method which can use the alkyl substituted α,β -unsaturated enones to provide the chiral 3,5-dialkyl pyrazolines in useful yield and enantioselectivity will afford a complementary way to bridge this gap and allow direct access to important classes of pyrazoline heterocycles (Scheme 1).^[19a]

First reported in 1968,^[19] 9-*epi*-aminocinchona alkaloids (**7**, Scheme 1) were found to serve as highly enantioselective organic catalysts during the last several years. To date, they have demonstrated high enantioselectivity in the promotion of a series of asymmetric conjugate additions of carbon,^[20] sulfur,^[21] nitrogen,^[22] and oxygen,^[23] nucleophiles to α,β -unsaturated carbonyl compounds, as well as of other nucleophilic additions^[24] and Diels-Alder reactions.^[25] Following our recent success in the development of **7**-catalyzed aminations^[22b] and peroxidations^[23d] of aliphatic α,β -enones, we became interested in developing the efficient enantioselective conjugate addition of hydrazide nucleophile **8** to aliphatic α,β -enones **9** followed by a deprotection-cyclization of the 1,4-adduct **10** as a catalytic asymmetric access to 2-pyrazolines **6** (Scheme 1).

We began our studies by selecting the appropriate hydrazide **8**, which was critical for the desired transformation, as the observed instability of **10** required mild deprotection conditions. Protecting the hydrazine with benzyl carbamate (Cbz) provided both the required regioselectivity and allowed the use of mild deprotection through hydrogenolysis. Benzyl substitution at the other hydrazine nitrogen made possible the cleavage of this group under hydrogenolysis conditions to form **6**.

For the promotion of the conjugate addition of an amine nucleophile via iminium catalysis, selection of an appropriate acid co-catalyst is crucial for achieving optimal reaction rate and enantioselectivity. Accordingly, a screening of several acids of varying acidity and steric properties was performed (Table 1) utilizing **9a** as a model substrate. As expected, there was no reaction observed after 15 hours without any acid co-catalyst (Entry 1, Table 1). Acetic acid (Entry 2), and several halogenated derivatives (Entries 3–5) revealed a trend of decreasing ee with increasing acidity; however, acceptable levels of conversion could not be obtained in conjunction with high ee. Two sterically hindered acetic acid derivatives (Entries 6–7) were investigated next, both of which afforded 76% and 86% ee, though not at a useful level when coupled with an acceptable reaction rate. Finally, benzoic acid (Entry 8) was used, giving an optimal combination of enantioselectivity and reaction rate. Lowering the equivalents of benzoic acid versus catalyst (Entries 9–10) decreased the reaction rate without decreasing selectivity, indicating that 3 equivalents of benzoic acid gave the best combination of ee and conversion.

We next screened the effect of solvent on the reaction (Table 2). Toluene, although a poor solvent for dissolving hydrazide **8**, proved to be one of the best for the asymmetric conjugate addition (Entry 1). Halogenated solvents, while fully dissolved all substrates, resulted in only moderate ee and conversion (Entries 2–4). Ethers, which also allowed full dissolution, gave generally moderate to high ee; however, conversions were significantly lower than with toluene (Entries 5–7). Following these results, and with the poor solubility of **8** in toluene in mind, several mixtures with chloroform (Entries 8–10) were investigated, all of

which improved solubility; however, decreased conversion. A mixed solvent of toluene and ether (Entry 11) maintained both excellent ee and good substrate solubility; however, the rate was slower in toluene. Finally, a mixture of toluene and 1,2-dichloroethane (Entry 12) provided improved substrate solubility along with a slight improvement in ee compared to pure toluene, while sacrificing a negligible level of conversion.

With optimized reaction conditions for the asymmetric conjugate addition, we decided to explore the deprotection-cyclization step. It was observed that due to the oxidative decomposition of N¹-benzylated 2-pyrazolines (cyclized product) the enantioselectivity was lower in comparison to aza-Michael adduct **10a**. We chose to stabilize 2-pyrazolines **6** by adding an electron-withdrawing acetyl group to the 1-position during cyclization. When subjected to deprotection-cyclization after acetyl substitution, the model substrate **9a** furnished 2-pyrazoline **6a** in 72% yield in two steps with no loss of ee compared to **10a** (Table 3, Entry 1 vs. Table 2, Entry 12).

We then investigated the scope of the reaction with regard to α,β -unsaturated enones **9** (Table 3). We found that a variety of alkyl substituents (R¹ and R²) with or without a functional group could be tolerated. Substrates with a methyl group as R¹, and R² either as ethyl (**9a**, Entries 1–2) or methyl group (**9b**, Entries 3–4) afforded good yield and selectivity, though enone **9b** showed slightly lower levels of ee than **9a**. Fixing R¹ as a methyl group, a variety of straight-chain aliphatic substrates were successfully applied in high ee. In addition to R¹ as *n*-propyl (**9c**, Entries 5–6) and *n*-pentyl (**9d**, Entries 7–8), the substrate scope included R¹ groups with a terminal chloride (**9e**, Entries 9–10), and a SEM-protected alcohol (**9f**, Entries 11–12), indicating compatibility with the use of protecting groups. Additionally, the methodology could be extended to enone **9g**, with straight-chain alkyl substituents at both R¹ and R² (Entries 13–14). Further, the enantiomer of **6a** was obtained in 83% ee by using catalyst **7-QD** (Table 3, Entry 2). This deprotection protocol could be applied to intermediates **10** to obtain 3,5-disubstituted 2-pyrazolines **6** in synthetically useful ee's and yields (Table 3). For all substrates, we observed similar isolated yields with both **7-Q** and **7-QD** catalyzed reactions; however, the ee of the product obtained with the **7-QD** pseudoenantiomer was consistently lower by 4 to 23% compared with that of the **7-Q**-catalyzed product. Importantly, in all cases either enantiomer could still be obtained in useful overall yield and enantiomeric excess.

In the presence of an acid co-catalyst, the 9-aminocinchona alkaloid **7** was postulated to activate the α,β -unsaturated enone **9** via iminium catalysis while interacting with the hydrazide **8** through hydrogen bonding in the stereo-defining step. Due to the presence of benzoic acid in the reaction mixture, the catalyst could exist as both the ammonium salt and the free amine. Thus, two modes of nucleophile activation by the catalyst-substrate iminium salt could be proposed (Scheme 2), both based on the bifunctional nature of 9-amino cinchona alkaloid catalysts. Mode A involves hydrogen bonding of the ammonium salt to substrate **8**. Although this mode decreases the nucleophilicity of **8** electronically, it promotes catalysis through bringing both reactants close to each other,^[26] facilitating the reaction while imparting stereocontrol. Three hydrogen bonding interactions are possible, involving the catalyst to interact with the carbonyl oxygen of the carbamate (mode A1), or with the nucleophilic nitrogen (mode A2). Additionally, the free amine catalyst can act as a base, activating nucleophile **8** via hydrogen bonding to the nucleophilic nitrogen (Mode B). As has been postulated previously,^[27] there exists the potential for nitrogen nucleophiles to compete with catalysts under iminium catalysis conditions through the formation of a nucleophile iminium salt; however, in this case no such background reaction was observed, indicating that the conjugate addition was promoted exclusively by the catalyst **7**.

In conclusion, we have developed an efficient enantioselective organocatalytic approach, which provides unprecedented asymmetric access to 3,5-dialkyl 2-pyrazolines **6** in useful yield and enantioselectivity. This methodology was tolerant of a variety of aliphatic α,β -unsaturated enones, using an easily accessible nitrogen nucleophile and catalyst. Additionally, both enantiomers of the chiral pyrazolines could be accessed by using the readily available bifunctional cinchona alkaloid catalysts derived from quinine (**7-Q**) and quinidine (**7-QD**). Such methodology should provide a useful asymmetric route to a variety of previously inaccessible asymmetric 3,5-dialkyl 2-pyrazolines and their derivatives.

Experimental Section

General Procedure for the Enantioselective Synthesis of Δ^2 -pyrazolines

Catalyst **7-Q** (4.9 mg, 15 μ mol) or **7-QD** (4.9 mg, 15 μ mol), benzoic acid (5.5 mg, 45 μ mol), and **8** (25.6 mg, 0.1 mmol) were dissolved in toluene/1,2-dichloroethane (7/3, 0.35 mL) in an ultrasonic bath for 5 minutes. The reaction vial was placed in a -25°C freezer for 20 minutes, at which point **9** (0.2 mmol) was added. After standing at -25°C for 4 days, the reaction mixture was purified by flash chromatography to give a mixture of **10** and **6** (inseparable mixture). This mixture was concentrated in vacuo and used for the formation of **6**.

To an oven-dried Schlenk flask under N_2 were added Pd/C (20 mg, 0.2 mmol, dry support) and **10** in THF (2.0 mL). The flask was cooled to -78°C , exchanged with H_2 , and AcCl (14 μ L, 0.2 mmol) was added. The bath was changed to -18°C (dry ice in saturated aqueous NaCl) and allowed to warm slowly to r.t. until the full consumption of **10** was observed by TLC (2–4 h). The reaction was stopped by passing the suspension through a Celite[®] plug with CHCl_3 . Solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with excess aqueous NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 1 mL), the combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The basified residue was purified by flash chromatography to give **6a–g** as pale yellow oils.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful for financial support from the National Institute of Health (GM-61591 and ARRA 3R01GM061591-09S1).

References

1. a) Ramalingam K, Thyvelikakath GX, Berlin KD. *J Med Chem.* 1977; 20:847. [PubMed: 406397]
b) Sharma PK, Kumar S, Kumar P, Kaushik P, Kaushik D, Dhingra Y, Aneja KR. *Eur J Med Chem.* 2010; 45:2650. [PubMed: 20171763]
2. Lombardino JG, Otterness IG. *J Med Chem.* 1981; 24:830. [PubMed: 7277388]
3. a) Coleman PJ, Schreier JD, Cox CD, Fraley ME, Garbaccio RM, Buser CA, Walsh ES, Hamilton K, Lobell RB, Rickert K, Tao W, Diehl RE, South VJ, Davide JP, Kohl NE, Yan Y, Kuo L, Prueksaritanont T, Li C, Mahan EA, Fernandez-Metzler C, Salata JJ, Hartman GD. *Bioorg Med Chem Lett.* 2007; 17:5390. [PubMed: 17761419] b) Shaharyar M, Abdullah MM, Bakht MA, Majeed J. *Eur J Med Chem.* 2010; 45:114. [PubMed: 19883957]
4. Prasad YR, Rao AL, Prasoon L, Murali K, Kumar PR. *Bioorg Med Chem Lett.* 2005; 15:5030. [PubMed: 16168645]
5. Lévai A. *J Heterocycl Chem.* 2002; 39:1.

6. a) Lange JHM, Stuijvenberg HHv, Veerman W, Wals HC, Stork B, Coolen HKAC, McCreary AC, Adolfs TJP, Kruse CG. *Bioorg Med Chem Lett*. 2005; 15:4794. [PubMed: 16140010] b) Srivastava BK, Joharapurkar A, Raval S, Patel JZ, Soni R, Raval P, Gite A, Goswami A, Sadhwani N, Gandhi N, Patel H, Mishra B, Solanki M, Pandey B, Jain MR, Patel PR. *J Med Chem*. 2007; 50:5951. [PubMed: 17979261] c) Lange JHM, Coolen HKAC, Stuijvenberg HHv, Dijkman JAR, Herremans AHJ, Ronken E, Keizer HG, Tipker K, McCreary AC, Veerman W, Wals HC, Stork B, Verveer PC, Hartog APd, Jong NMJd, Adolfs TJP, Hoogendoorn J, Kruse CG. *J Med Chem*. 2004; 47:627. [PubMed: 14736243]
7. Elguero, J. *Comprehensive Heterocyclic Chemistry*. Katritzky, AR.; Rees, CW., editors. Vol. 5. Pergamon; Oxford: 1984. p. 167
8. a) Cox CD, Torrent M, Breslin MJ, Mariano BJ, Whitman DB, Coleman PJ, Buser CA, Walsh ES, Hamilton K, Schaber MD, Lobell RB, Tao WK, South VJ, Kohl NE, Yan YW, Kuo LC, Prueksaritanont T, Slaughter DE, Li CZ, Mahan E, Lu B, Hartman GD. *Bioorg Med Chem Lett*. 2006; 16:3175. [PubMed: 16603356] (b) Cox CD, Breslin MJ, Mariano BJ, Coleman PJ, Buser CA, Walsh ES, Hamilton K, Huber HE, Kohl NE, Torrent M, Yan Y, Kuo LC, Hartman GD. *Bioorg Med Chem Lett*. 2005; 15:2041. [PubMed: 15808464] (c) Cox CD, Breslin MJ, Mariano BJ. *Tetrahedron Lett*. 2004; 45:1489.
9. a) Santos, JMD; López, Y.; Aparicio, D.; Palacios, F. *J Org Chem*. 2008; 73:550. [PubMed: 18085795] b) Guerra FM, Mish MR, Carreira EM. *Org Lett*. 2000; 2:4265. [PubMed: 11150215]
10. Mish MR, Guerra FM, Carreira EM. *J Am Chem Soc*. 1997; 119:8379.
11. a) Weinhardt K, Wallach MB, Marx M. *J Med Chem*. 1985; 28:694. [PubMed: 4009590] b) Bielmeyer P, Kaiser A, Gust R, Wiegreb W. *Monatsh Chem*. 1996; 127:1073. c) Kaiser A, Bielmeyer P, Wiegreb W. *Monatsh Chem*. 1997; 128:1247.
12. Meyers MJ, Arhancet GB, Hockerman SL, Chen X, Long SA, Mahoney MW, Rico JR, Garland DJ, Blinn JR, Collins JT, Yang S, Huang HC, McGee KF, Wendling JM, Dietz JD, Payne MA, Homer BL, Heron MI, Reitz DB, Hu X. *J Med Chem*. 2010; 53:5979. [PubMed: 20672822]
13. Kanemasa S, Kanai T. *J Am Chem Soc*. 2000; 122:10710.
14. Zielinska-Błajet M, Kowalczyk R, Skar ewski J. *Tetrahedron*. 2005; 61:5235.
15. [3+2] cycloadditions with diazoesters: Kano T, Hashimoto T, Maruoka K. *J Am Chem Soc*. 2006; 128:2174. [PubMed: 16478146] Sibi MP, Standley LM, Soeta T. *Org Lett*. 2007; 9:1553. [PubMed: 17367154] Gao L, Hwang GS, Lee MY, Ryu DH. *Chem Commun*. 2009:5460.
16. [3+2] cycloadditions with nitrilimines: Sibi MP, Stanley LM, Jasperse CP. *J Am Chem Soc*. 2005; 127:8276. [PubMed: 15941248] Sibi MP, Stanley LM, Soeta T. *Adv Synth Catal*. 2006; 348:2371.
17. Müller S, List B. *Angew Chem, Int Ed*. 2009; 48:9975.
18. Mahé O, Dez I, Levacher V, Brière JF. *Angew Chem, Int Ed*. 2010; 49:7072.
19. Pettit GR, Gupta SK. *J Chem Soc C*. 1968:1208.
20. a) Xie JW, Yue L, Chen W, Du W, Zhu J, Deng JG, Chen YC. *Org Lett*. 2007; 9:413. [PubMed: 17249775] b) Xie JW, Chen W, Li R, Zeng M, Du W, Yue L, Chen YC, Yong W, Zhu J, Deng JG. *Angew Chem, Int Ed*. 2007; 46:389. c) Chen W, Du W, Yue L, Li R, Wu Y, Ding LS, Chen YC. *Org Biomol Chem*. 2007; 5:816. [PubMed: 17315068] d) Bartoli G, Bosco M, Carlone A, Pesciaoli F, Sambri L, Melchiorre P. *Org Lett*. 2007; 9:1403. [PubMed: 17346059]
21. Ricci P, Carlone A, Bartoli G, Bosco M, Sambri L, Melchiorre P. *Adv Synth Catal*. 2008; 350:49.
22. a) Pesciaoli F, Vincentiis FD, Galzerano P, Bencivenni G, Bartoli G, Mazzanti A, Melchiorre P. *Angew Chem, Int Ed*. 2008; 47:8703. b) Lu X, Deng L. *Angew Chem, Int Ed*. 2008; 47:7710. c) Gogoi S, Zhao CG, Ding D. *Org Lett*. 2009; 11:2249. [PubMed: 19415906]
23. a) Reisinger CM, Wang X, List B. *Angew Chem, Int Ed*. 2008; 47:8112. b) Carlone A, Bartoli G, Bosco M, Pesciaoli F, Ricci P, Sambri L, Melchiorre P. *Eur J Org Chem*. 2007:5492. c) Wang X, Reisinger CM, List B. *J Am Chem Soc*. 2008; 130:6070. [PubMed: 18422314] d) Lu X, Liu Y, Sun B, Cindric B, Deng L. *J Am Chem Soc*. 2008; 130:8134. [PubMed: 18529055]
24. a) McCooley SH, Connon SJ. *Org Lett*. 2007; 9:599. [PubMed: 17243708] b) Liu TY, Cui HL, Zhang Y, Jiang K, Du W, He ZQ, Chen YC. *Org Lett*. 2007; 9:3671. [PubMed: 17691800]
25. Singh RP, Bartelsson K, Wang Y, Su H, Lu X, Deng L. *J Am Chem Soc*. 2008; 130:2422. [PubMed: 18251543]

26. Silverman, RB. The Organic Chemistry of Enzyme-Catalyzed Reactions. Academic Press; San Diego: 2000.
27. Perdicchia D, Jørgensen KA. J Org Chem. 2007; 72:3565. [PubMed: 17391046]

Figure 1.
2-pyrazolines with valuable biological-activities

Scheme 1.
Synthetic route to 3,5-disubstituted pyrazolines **6** and 9-aminocinchona alkaloid catalysts **7-Q** and **7-QD**.

Scheme 2.

Proposed Modes of substrate activation by catalyst **7**, and potential substrate-activated mode of background catalysis.

Table 1

Acid co-catalyst screening.^[a]

Entry	Acid	Equiv. vs. 7-Q	Conv. [%] ^[b]	ee 10a [%]
1	-	-	0	-
2	CH ₃ CO ₂ H	3	3	85
3	ClCH ₂ CO ₂ H	3	3	37
4	Cl ₂ CHCO ₂ H	3	33	7
5	CF ₃ CO ₂ H	3	15	racemic
6	Ph ₂ CHCO ₂ H	3	12	76
7	Ph ₃ CCO ₂ H	3	3	86
8	PhCO ₂ H	3	12	90
9	PhCO ₂ H	2	9	91
10	PhCO ₂ H	1	2	-

^[a] **8** (0.05 mmol) and **9a** (0.1 mmol).^[b] For comparative purposes only, determined by relative integration of **8** and **10a** on GC.

Table 2

Solvent screening for the addition of **8** to **9a**.^[a]

Entry	Solvent	Conv. [%] ^[b]	ee 10a [%]
1	Toluene	51	88
2	CHCl ₃	13	76
3	1,2-dichloroethane	22	77
4	CH ₂ Cl ₂	13	82
5	THF	8	82
6	TBME	21	88
7	Et ₂ O	24	91
8 ^[c]	Toluene/CHCl ₃ (7/3)	40	87
9 ^[c]	Mesitylene/CHCl ₃ (7/3)	33	89
10 ^[c]	Et ₂ O/CHCl ₃ (7/3)	35	89
11	Toluene/Et ₂ O (1/1)	31	91
12 ^[c]	Toluene/1,2-DCE	47	90

^[a] Reaction conditions: **8** (0.05 mmol) and **9a** (0.1 mmol), and solvent (0.18 mL).^[b] For comparative purposes only, determined by relative integration of **8** and **10a** on GC.^[c] Solvent (0.2 mL).

Table 3

Substrate scope for the addition of **8** to enones **9a-f**.^[a]

Entry	R ¹ /R ²	9 – 6	7	Yield 6 [%](2 steps)	ee 6 [%]
1	Me/Et	9a-6a	7-Q	72	90
2	Me/Et	9a-6a	7-QD	60	83
3	Me/Me	9b-6b	7-Q	57	82
4	Me/Me	9b-6b	7-QD	46	59
5	<i>n</i> -Pr/Me	9c-6c	7-Q	78	90
6	<i>n</i> -Pr/Me	9c-6c	7-QD	74	81
7	<i>n</i> -Pen/Me	9d-6d	7-Q	58	82
8	<i>n</i> -Pen/Me	9d-6d	7-QD	63	76
9	Cl(CH ₂) ₃ /Me	9e-6e	7-Q	50	91
10	Cl(CH ₂) ₃ /Me	9e-6e	7-QD	63	75
11	SEMO(CH ₂) ₃ /Me	9f-6f	7-Q	64	91
12	SEMO(CH ₂) ₃ /Me	9f-6f	7-QD	66	76
13	<i>n</i> -Pr/ <i>n</i> -Bu	9g-6g	7-Q	66	90
14	<i>n</i> -Pr/ <i>n</i> -Bu	9g-6g	7-QD	72	86

^[a]Reaction conditions (a): **8** (0.1 mmol) **9** (0.2 mmol), **7** (15 mol%), PhCO₂H (45 mol%), and solvent (0.35 mL); (b): AcCl (0.2 mmol), Pd/C (20 mg), and THF (2.0 mL).